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VOLUME 99 — SEPTEMBER 1990
Number 9, Part 1 (Issued in 2 Parts)

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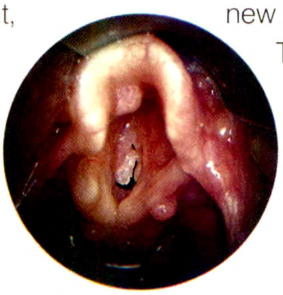

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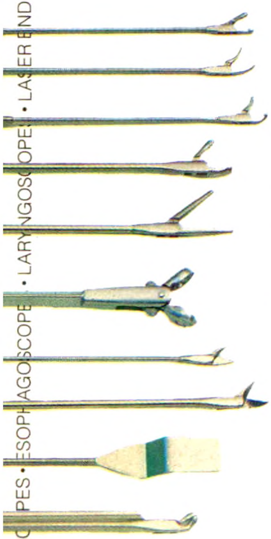

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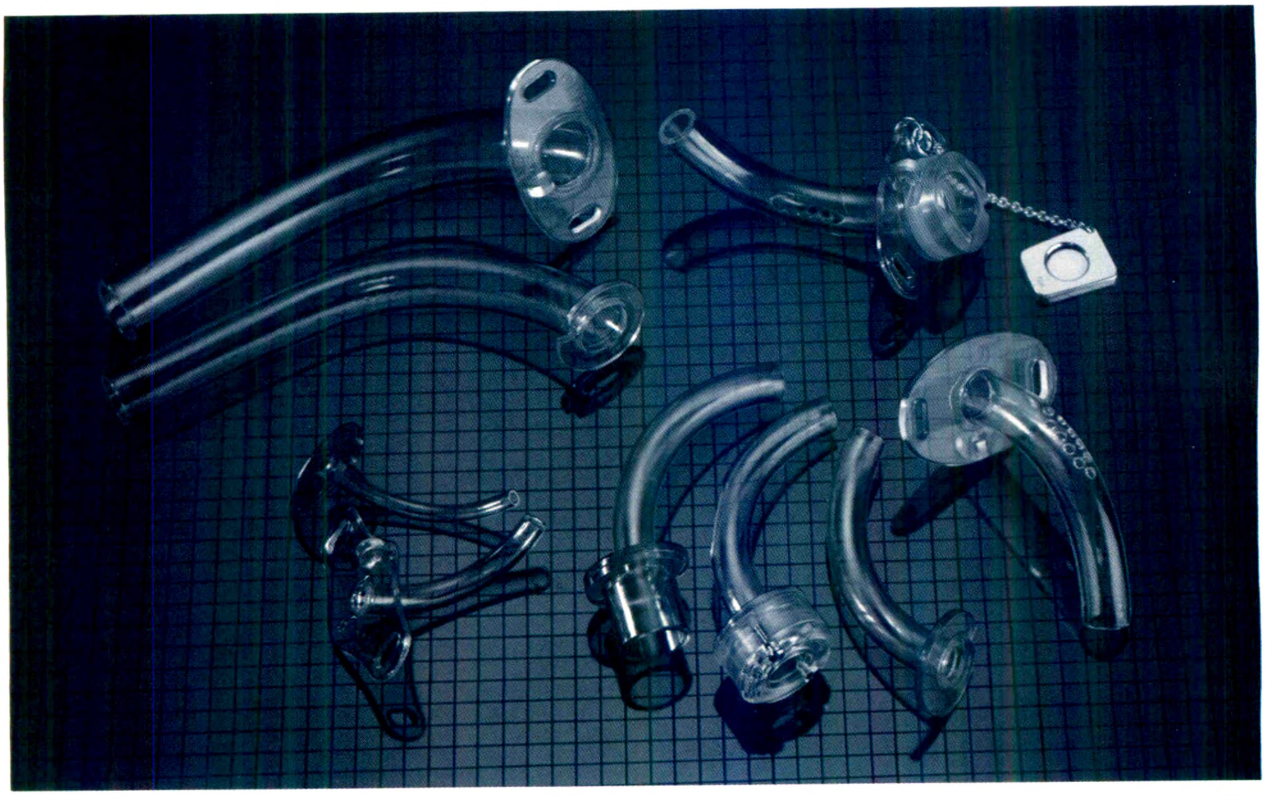

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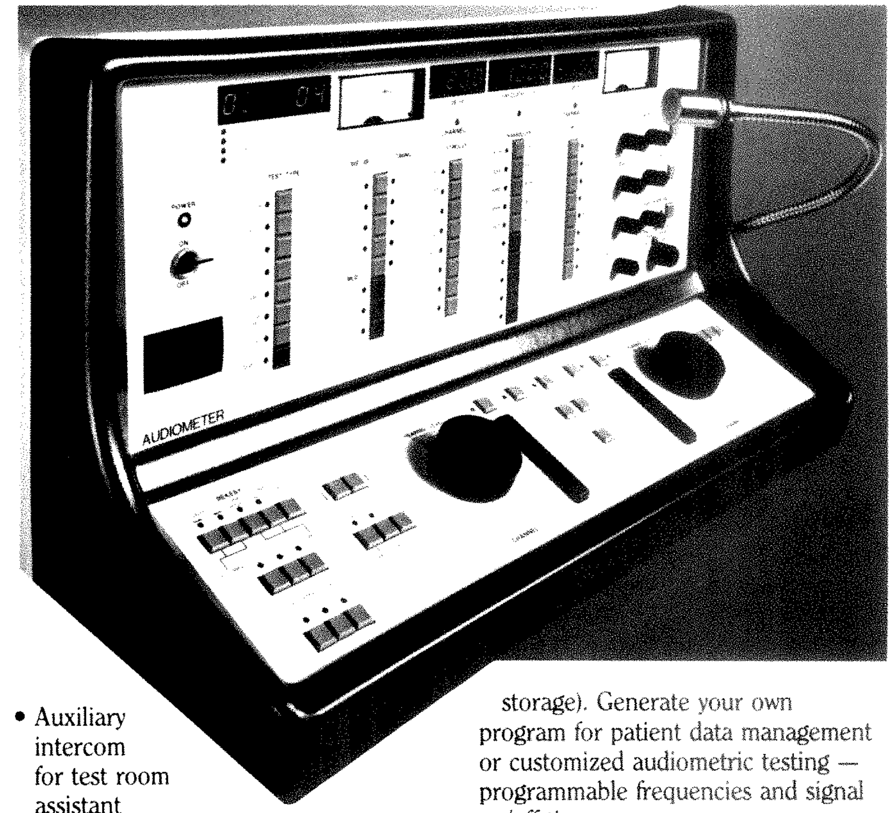

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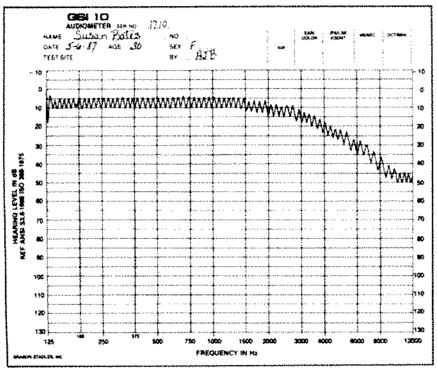

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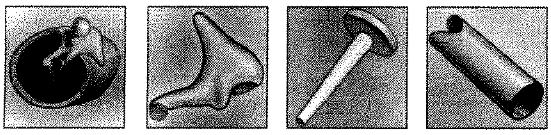

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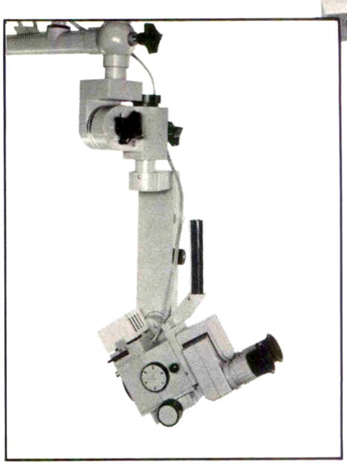

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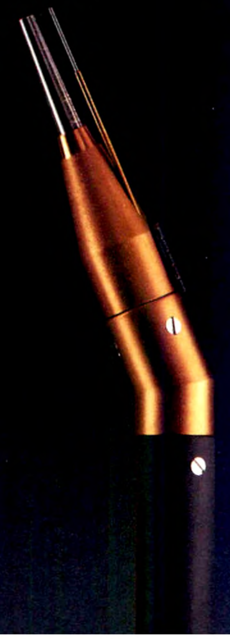

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SULCUS VOCALIS: FUNCTIONAL ASPECTS

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The vocal function of 126 patients with sulcus vocalis was evaluated with the use of a test battery of multidimensional evaluation items. Of the 126 patients, 31 had a unilateral sulcus and 95, bilateral lesions. The results were as follows. 1) The majority of the patients had a mild degree of hoarseness with a breathy quality. 2) An incomplete glottic closure, a small vibratory amplitude, and a small mucosal wave were frequently observed in the stroboscopic examination. 3) The maximum phonation time, fundamental frequency range, and sound pressure level range of phonation were decreased, whereas the airflow during phonation was increased. 4) The pitch perturbation quotient, amplitude perturbation quotient, and normalized noise energy were increased. 5) Abnormal test results were more frequent and more marked for bilateral lesions than for unilateral lesions.

KEY WORDS — dysphonia, sulcus vocalis, vocal function.

Recent technical advances in laryngeal examination including fiberoscopy, microscopy, and videostroboscopy have facilitated visualization of minor lesions of the larynx that had been frequently overlooked with the traditional laryngeal mirror examination. Sulcus vocalis is one of those minor lesions that is apt to be missed. It is not a very rare disease[1-7] and it causes various degrees of dysphonia. The most typical clinical manifestations of sulcus vocalis are hoarseness, bowing of the vocal fold edge, a spindle-shaped glottic gap during phonation, and the existence of a furrow along the vocal fold edge. The ventricular folds are frequently overadducted during phonation in an attempt to compensate for the glottic incompetence. The lesion can be unilateral or bilateral.

Some functional aspects of this disease entity have been reported on the basis of rather small numbers of patients.[2,4,5] Since the vocal function is multidimensional, more comprehensive studies have been demanded in order to elucidate all aspects of dysphonia caused by sulcus vocalis. Such information is relevant to improving treatment modalities for the disease. Hirano conducted an extensive investigation on objective clinical evaluation of the human voice in which the vocal function of patients with sulcus vocalis was studied.[8] However, sulcus vocalis was not the primary focus in his study. The purpose of this paper was to investigate the comprehensive features of the voice disorder caused by sulcus vocalis on the basis of analyses of a large number of patients.

SUBJECTS AND METHODS

The subjects of this study were 126 adult patients, 101 men and 25 women with sulcus vocalis, who underwent a set of vocal examinations from 1983 to 1987 at the Department of Otolaryngology-Head and Neck Surgery, Kurume University Hospital. The lesion was unilateral in 31 patients (23 men and 8 women) and bilateral in 95 (78 men and 17 women). Table 1 shows the distribution of the patients by age, sex, and laterality. The ages ranged from 24 to 79 years (mean, 61 years). The majority of the patients were over 50 years of age. Those patients who had additional laryngeal disorders, including inflammation, polyps, edema, paralysis, and neoplasms, were excluded from the present series.

The test battery employed for vocal examinations consisted of perceptual evaluation of hoarseness by means of the GRBAS (grade, rough, breathy, asthenic, strained) scale; video fiberstroboscopy; physiologic examination including measurements of the maximum phonation time (MPT), mean airflow rate during phonation over comfortable duration (MFRc), fundamental frequency (F0) range and sound pressure level (SPL) range of phonation; and acoustic analyses of tape-recorded voice.[9] Maximum phonation time, MFRc, F0 range, and SPL range were measured by means of the Nagashima PS-77H, an apparatus for simultaneous recordings of the F0, SPL, airflow, and air volume. As a result, the measurements were conducted while the pa-

TABLE 1. DISTRIBUTION OF 126 PATIENTS WITH SULCUS VOCALIS BY AGE, SEX, AND LATERALITY

	Men		*Women*		
Age (yr)	*U*	*B*	*U*	*B*	*Total Pts*
20-29	1	2	0	1	4
30-39	2	3	0	1	6
40-49	1	6	0	2	9
50-59	5	18	1	3	27
60-69	11	22	3	4	40
70-79	3	27	4	6	40
Total	23	78	8	17	126

U — unilateral, B — bilateral.

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Presented at the meeting of the American Broncho-Esophagological Association, Palm Beach, Florida, May 2-3, 1990.

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TABLE 2. RESULTS OF PERCEPTUAL EVALUATION OF HOARSENESS BY MEANS OF GRBAS SCALE

GRBAS Scale	*U*	*B*	*Total*
Grade			
0	9	19	28 (23%)
1	16	66	82 (68%)
2	2	8	10 (8%)
3	0	1	1 (1%)
Rough			
0	20	55	75 (62%)
1	6	37	43 (36%)
2	1	2	3 (2%)
3	0	0	0
Breathy			
0	10	24	34 (28%)
1	15	63	78 (64%)
2	2	6	8 (7%)
3	0	1	1 (1%)
Asthenic			
0	25	78	103 (85%)
1	2	15	17 (14%)
2	0	1	1 (1%)
3	0	0	0
Strained			
0	26	79	105 (87%)
1	1	14	15 (12%)
2	0	1	1 (1%)
3	0	0	0

Data were not available in five cases.

GRBAS — grade, rough, breathy, asthenic, strained; U — unilateral, B — bilateral, 0 — none, 1 — mild, 2 — moderate, 3 — severe.

tients phonated into a mouthpiece attached to the apparatus. The MPT and the Fo range measured in this way do not differ significantly from those measured without a mouthpiece. However, the SPL range determined in this way is smaller than that measured without a mouthpiece by approximately 10 dB.[8] In the acoustic analyses, pitch perturbation quotient (PPQ), amplitude perturbation quotient (APQ), normalized noise energy for the frequency band 0 to 4 kHz (NNEa), and normalized noise energy for the frequency band 1 to 4 kHz (NNEb) were determined for the sustained /e/ vowel with the technique by Kasuya et al[10] and Kikuchi et al.[11]

Standard statistical analyses including determination of the mean, standard deviation, and correlation coefficient and the *t* test were performed. For the values of MPT, MFRc, Fo, PPQ, and APQ, logarithmic transformation was applied.

RESULTS

Perceptual Evaluation. Table 2 shows the results of perceptual evaluation of hoarseness. The majority of the patients had a mild grade of hoarseness. The breathy voice quality was frequently noted, the rough quality was occasionally found, and the asthenic quality and strained voice quality were infrequently recognized. Hoarseness was more frequent and more marked for the bilateral lesions than for the unilateral lesions.

TABLE 3. RESULTS OF VIDEO FIBERSTROBOSCOPY

	U	*B*
Symmetry		
Symmetric	13	55
Asymmetric	14	32
Regularity		
Regular	23	75
Inconsistent	2	3
Irregular	2	9
Glottic closure		
Complete	15	27
Inconsistent	0	3
Incomplete	12	57
Amplitude		
Great	0	3
Normal	11	26
Small	16	58
Mucosal wave		
Normal	9	21
Small	18	63
None	0	3

Data were not available on 12 patients.

U — unilateral, B — bilateral.

Video Fiberstroboscopy. Table 3 presents the results of video fiberstroboscopy. The most frequent abnormal findings were an incomplete glottic closure during vibratory cycles, a small amplitude of vibration, and a small mucosal wave. These results were observed more frequently for the bilateral lesions than for the unilateral lesions. The mucosal wave frequently was not propagated across the sulcus.

Physiologic Correlates. Maximum phonation time ranged from 9.7 to 47.0 seconds with a mean of 18.1 seconds for the unilateral lesions, and from 2.5 to 40.0 seconds with a mean of 13.1 seconds for the bilateral lesions. The difference between the two groups was statistically significant ($p<.01$). Figure 1A depicts the histogram of MPT. Maximum phonation time was shorter than 20 seconds (an approximate average for normal adults) in the majority of the cases. It was shorter than 10 seconds (the lower limit for the normal population) in a considerable number of cases of bilateral sulci.

The MFRc measured 63 to 306 mL/s with a mean of 148 mL/s in the cases of unilateral sulcus, and 83 to 476 mL/s with a mean of 195 mL/s in the cases of bilateral sulci. The difference between the two groups was statistically significant ($p<.01$). As shown in Fig 1B, the majority of the patients presented an MFRc value greater than 120 mL/s (an approximate mean value for normal adults). The MFRc was greater than 250 mL/s (an approximate upper limit for normal adults) in some patients with bilateral lesions.

The Fo range of phonation measured 11 to 38 semitones with a mean of 22.7 semitones for the unilateral lesions, and 5 to 38 semitones with a

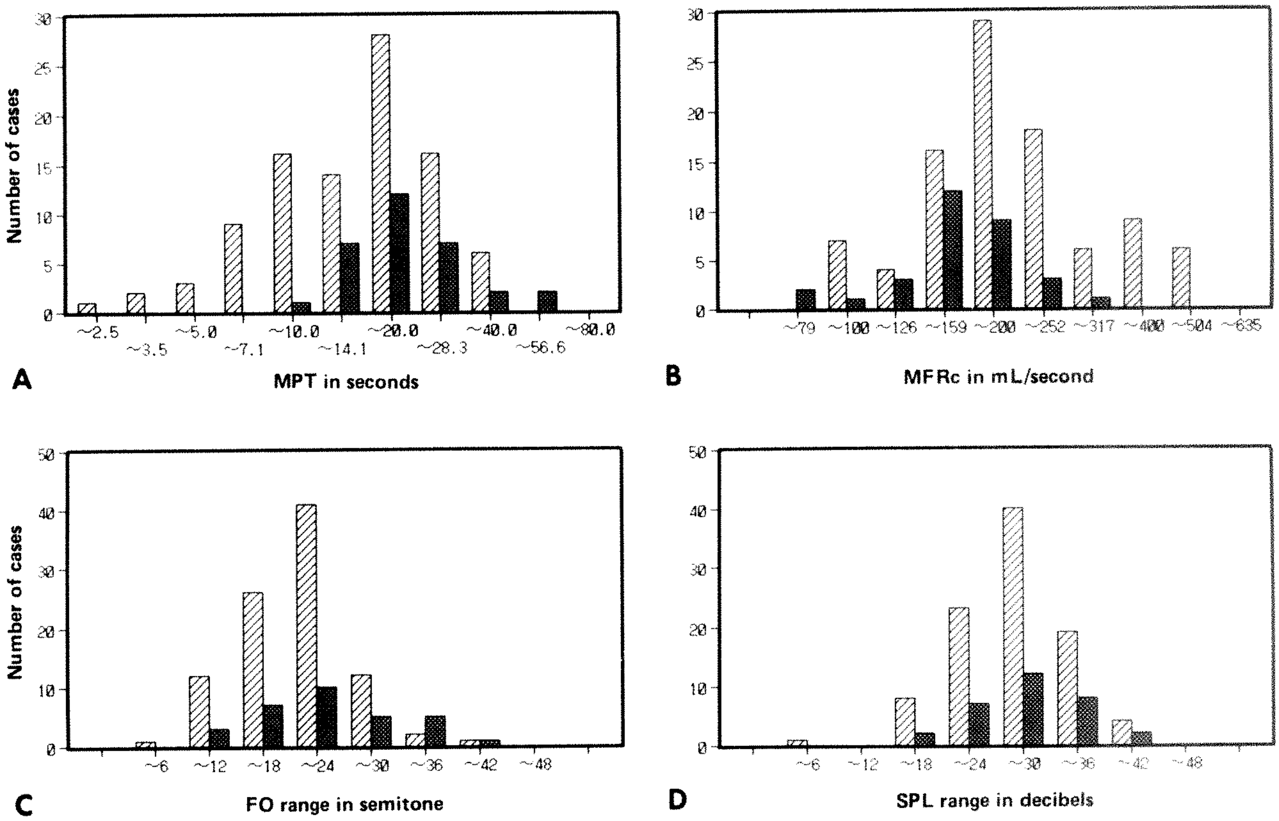

Fig 1. Histograms of A) maximum phonation time (MPT), B) mean airflow rate during phonation over comfortable duration (MFRc), C) fundamental frequency (F0) range, and D) sound pressure level (SPL) range. Cross-hatched bars — unilateral lesions, diagonally shaded bars — bilateral lesions.

mean of 19.4 semitones for the bilateral lesions. The difference between the two groups was statistically significant ($.01 < p < .02$). As shown in Fig 1C, most patients presented an F0 range smaller than 30 semitones (an approximate average value for normal adults), and some showed an F0 range smaller than 18 semitones (an approximate lower limit for the normal population). Limited F0 ranges were observed more frequently in the patients with bilateral sulci than in those with a unilateral lesion.

The SPL range of phonation ranged from 13 to 38 dB with a mean of 28.1 dB for the unilateral group, and from 6 to 42 dB with a mean of 26.6 dB for the bilateral group. There was no significant difference in SPL range between the two groups. As shown in Fig 1D the SPL range was smaller than 33 dB (an approximate average for normal adults) in the majority of the cases, and it was smaller than 24 dB (an approximate lower limit of normal subjects) in some patients.

Acoustic Analyses. Pitch perturbation quotient ranged from 0.05% to 1.82% with a mean of 0.22% for the unilateral lesions, and from 0.11% to 3.15% with a mean of 0.30% for the bilateral lesions. There was no statistically significant difference in PPQ between the two groups. As shown in Fig 2A, PPQ was within normal range (approximately 0.5% or less) in the majority of the cases. Some patients presented a high PPQ.

The APQ measured 0.18% to 5.83% with a mean of 1.16% in the unilateral group, whereas it ranged from 0.43% to 14.5% with a mean of 1.65% in the bilateral group. The difference between the two groups was statistically significant ($.02 < p < .05$). The APQ value was greater than 1.5% (an approximate upper limit for the normal population) in many patients with bilateral sulci and in some patients with a unilateral lesion (Fig 2B).

Normalized noise energy for the frequency band 0 to 4 kHz ranged from −32.8 to −8.6 dB with a mean of −22.6 dB in the unilateral group, and from −31.1 to −6.9 dB with a mean of −21.1 dB in the bilateral group. There was no significant difference in NNEa between the two groups. The NNEa value was greater than −22.5 dB (an approximate upper limit for the normal population) in some cases (Fig 2C).

Normalized noise energy for the frequency band 1 to 4 kHz measured −21.5 to −1.3 dB with a mean of −10.9 dB in the patients with a unilateral lesion, whereas it ranged from −17.1 to −0.6 dB with a mean of −6.8 dB in the patients with bilateral lesions. The NNEb was significantly greater for the bilateral lesions than for the unilateral lesions ($p < .01$). The NNEb value was greater than −13.5 dB (an approximate upper limit for the normal population) in most cases of bilateral sulci and in many of the unilateral cases.

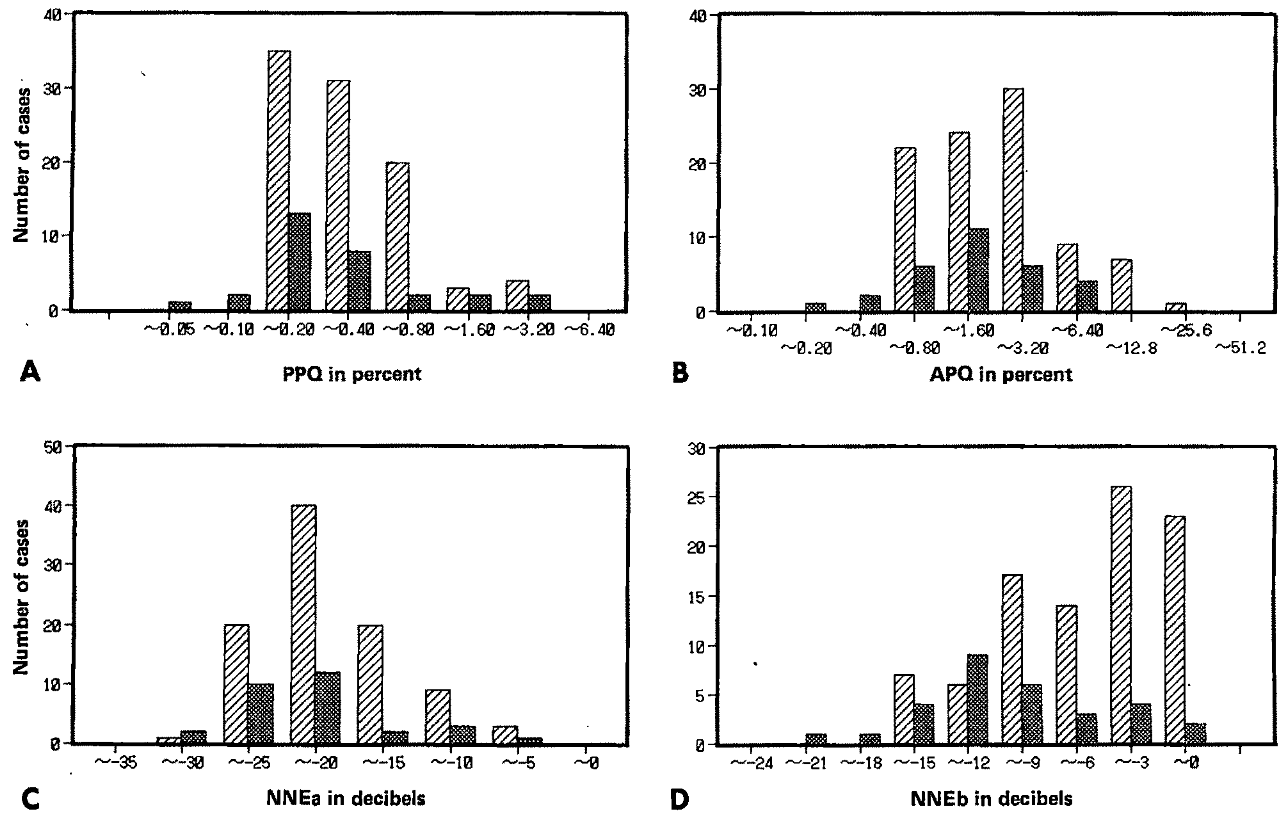

Fig 2. Histograms of A) pitch perturbation quotient (PPQ), B) amplitude perturbation quotient (APQ), C) normalized noise energy for frequency band 0 to 4 kHz (NNEa), and D) normalized noise energy for frequency band 1 to 4 kHz (NNEb). Cross-hatched bars — unilateral lesions, diagonally shaded bars — bilateral lesions.

Correlation Between Test Items. Table 4 presents the correlation coefficients between the measured values of the different tests employed. Between the physiologic correlates, MPT was negatively correlated to MFRc and positively correlated to the F0 range. The F0 range and SPL range were positively correlated to each other. These correlations were of moderate degree. There were high positive correlations between PPQ, APQ, and NNEa. Normalized noise energy for the frequency band 1 to 4 kHz was positively correlated to PPQ, APQ, and NNEa, and the degree of the correlations was moderate. The correlations between the physiologic correlates and the acoustic correlates were low. Normalized noise energy for the frequency band 1 to 4 kHz was negatively correlated to MPT and positively correlated to MFRc.

DISCUSSION

From a pathophysiologic point of view, the features of the sulcus vocalis consist of 1) a bowing of the vocal fold edge, 2) an increase in stiffness of the vibratory tissue of the vocal fold, and 3) a deformity of the vocal fold edge resulting from the presence of a sulcus. Histopathologically, the sulcus vocalis is usually located in the superficial layer of the lamina propria or the Reinke space at the vocal fold edge, and an increase in collagenous fibers is often observed around the sulcus.[3,4,12]

The bowing of the vocal fold edge results in an incomplete glottic closure during vibratory cycles. This was frequently observed in the stroboscopic examination in this study, especially in the patients with bilateral lesions. The increase in stiffness of the vibratory tissue causes limited vibratory movements of the vocal fold edge during phonation, which have been manifested in a small vibratory amplitude and a small mucosal wave in the stroboscopic examination of the present series. The stiffness contributes also to the incomplete glottic closure during vibratory cycles. The deformity of the vocal fold edge from the existence of the sulcus interferes with a smooth propagation of the mucosal waves. This also contributes to an incomplete glottic closure.

The glottic incompetence during phonation causes a decrease in MPT and an increase in MFRc, NNEa, and NNEb, as has been shown in the present results. The degree of the glottic incompetence in the cases of sulcus vocalis is usually not very high. A tiny glottic gap during phonation associated with a stiff vocal fold tissue tends to cause high-frequency noise. This was shown in that an increase in NNEb was more frequent and more marked than that in NNEa in the present series. The increase in NNEb was perceptually noted as a hoarse voice with a breathy quality.

The F0 range and SPL range of phonation tended

TABLE 4. CORRELATION COEFFICIENT

	MPT	*MFRc*	*F0 Range*	*SPL Range*
Between physiologic correlates (n = 126)				
MPT		−0.518	0.465	0.269
MFRc			−0.161	0.068
F0 range				0.482
SPL range				
	PPQ	*APQ*	*NNEa*	*NNEb*
Between acoustic correlates (n = 123)				
PPQ		0.745	0.816	0.605
APQ			0.799	0.627
NNEa				0.567
NNEb				
	PPQ	*APQ*	*NNEa*	*NNEb*
Between physiologic and acoustic correlates (n = 123)				
MPT	−0.175	−0.208	−0.065	−0.377
MFRc	0.062	0.077	−0.010	0.339
F0 range	−0.233	−0.297	−0.252	−0.285
SPL range	−0.247	−0.191	−0.214	−0.179

Data on acoustic correlates were not available for three patients.

MPT — maximum phonation time, MFRc — mean airflow rate during phonation over comfortable duration, F0 — fundamental frequency, SPL — sound pressure level, PPQ — pitch perturbation quotient, APQ — amplitude perturbation quotient, NNEa — normalized noise energy for frequency band 0 to 4 kHz, NNEb — normalized noise energy for frequency band 1 to 4 kHz.

to decrease in the present series. This can be also attributed to the glottic incompetence during phonation and the stiff vocal fold tissue.

Regular or periodic vibrations were observed under stroboscopy in the majority of the patients of the present investigation. Basically, stroboscopy cannot detect slightly irregular or aperiodic vibrations. The PPQ and APQ are more sensitive to aperiodic vibrations than is stroboscopy. In the present series, abnormally great APQ and PPQ values were found more frequently than stroboscopically irregular vibrations, indicating that vocal folds with a sulcus tend to display slightly irregular vibrations. The occurrence of abnormally high values was more frequent for APQ than for PPQ. In other words, the amplitude of the waveform was more aperiodic than the pitch period.

There have been no consistently effective treatment modalities for sulcus vocalis, although several attempts have been reported.[3,4,5,7,13,14] The results of the present investigation showed that all three pathophysiologic features described earlier were reflected in abnormal test values. The ideal treatment, therefore, should be elimination of the three pathophysiologic problems. The bowing of the vocal fold edge can be corrected by means of intrafold injection. Intrafold injections improve the voice to a greater or lesser extent in about three fourths of patients, but they usually do not yield a normal voice.[4,6,14] Elimination of the stiff tissue around the sulcus and correction of the deformed vocal fold edge should be achieved in order to recover a normal voice. This is one of the unsolved problems in modern phonosurgery.

Finally, it should be emphasized that a set of vocal function tests are necessary to determine the degree of dysphonia caused by sulcus vocalis and to evaluate the effects of any treatments for sulcus vocalis.

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Ann Otol Rhinol Laryngol 99:1990

MANAGEMENT OF SHARP AND PENETRATING FOREIGN BODIES OF THE UPPER AERODIGESTIVE TRACT

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The aspiration or ingestion of a foreign body into the upper aerodigestive tract is a common accident that befalls children and adults alike. Sharp and pointed objects pose special problems. The basic principles of their extraction were meticulously developed by Chevalier Jackson, whose concepts of the mechanical problems encountered and demonstrations of their solutions are responsible for keeping morbidity and mortality figures at a minimum. The principles of evaluation and management of sharp and penetrating foreign bodies of the upper digestive tract are described.

KEY WORDS — esophageal perforation, foreign body.

INTRODUCTION

In general, the treatment of choice for foreign bodies in the upper aerodigestive tract is reasonably prompt endoscopic removal under conditions of maximum safety and minimum trauma. Too often, foreign body aspirations and ingestions are considered urgent or emergencies, leading to hasty, inadequate study and poorly prepared, improper attempts at removal. The majority of patients with foreign bodies who are evaluated by the otolaryngologist already have passed the acute phase. When there is no urgent danger to the patient's life, the problem can be approached with complete and thoughtful consideration of the physiologic and mechanical factors involved. Endoscopic removal can be scheduled when trained personnel are available, instruments have been checked, and techniques have been tested.

The presence of a sharp or pointed foreign object, threateningly dramatized on a radiograph and compounded by parents' and referring physicians' anxiety, must not be permitted to exert pressure on the endoscopist to act precipitously before necessary preparations are made. However, untoward delay in removing the foreign body can also be harmful. Endoscopy, therefore, is deferred only until preoperative studies have been performed and the patient has been prepared optimally for the operation by adequate hydration, emptying of the stomach, and so forth.

The four situations that are considered urgent are as follows.

1. Actual or potential airway obstruction. Foreign bodies in the larynx or tracheobronchial tree are removed the same day the diagnosis is made.

2. Esophageal perforation or imminent perforation.

3. Disc battery ingestion with esophageal lodgment. Within 4 hours of ingestion, leakage of caustic battery contents may lead to erosion through the esophageal wall.[1]

4. Aspiration of dried beans or peas into the airway. A major bronchus may be obstructed for a day until absorbed moisture finally bursts the capsule and the child asphyxiates as the bean rapidly swells to occlude the trachea.

Sharp objects may occur as foreign bodies in either of the first two urgent situations: airway obstruction or esophageal perforation. If perforation has already occurred, management of the perforation becomes the primary consideration, with removal of the foreign body dependent upon the patient's condition.

PREOPERATIVE EVALUATION AND PREPARATION

Adequate preparation for foreign body extraction involves four basic steps.

1. The patient is evaluated and prepared. 1) Radiographs in three planes: posteroanterior, lateral, and the greatest plane of the foreign body. A contrast study is rarely indicated, but may be considered if a nonradiopaque object is suspected but not localized, or if a perforation is suspected. 2) Nothing by mouth for 6 hours. 3) Adequate hydration.

2. Evaluation and analysis of a duplicate foreign body. If one is unavailable, parents are asked to return home to locate one. An alternative is to have them draw the best likeness possible.

3. The duplicate object is examined and manipulated with both forceps and scopes to practice the retrieval technique and to evaluate how the object behaves with various types and applications of forceps.

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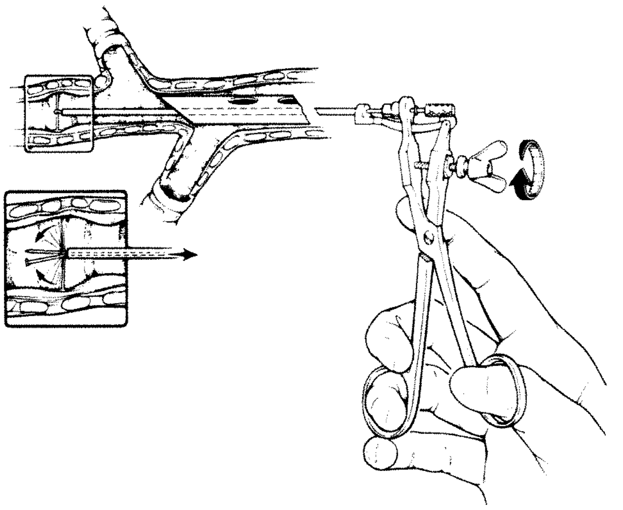

Fig 1. Pin-bending forceps particularly for use with bendable pins in lung periphery. Pin is grasped in midportion of stem by heavy rotation-type blades and bent as it is drawn into cannula. Heavy handle has wing nut to apply mechanical advantage necessary to bend pin.

4. Surgical, anesthesia, and nursing teams are assembled. Instruments are prepared.

Rigid (open-tube) endoscopes are the instruments of choice with rare exceptions. Following induction of anesthesia, the scope is introduced and the presentation of the object is studied 1) to determine the relationship to surrounding tissues and structures, 2) to evaluate the position of the unseen portion of the foreign body, 3) to evaluate the best forceps to use, and 4) to locate adequate forceps spaces.

The tip of the endoscope may be used to manipulate the foreign body to effect a more favorable presentation, to retract tissue, to create forceps spaces, and to protect the grasp of the forceps.

A gastric or duodenal foreign body is more amenable to extraction with a flexible fiberoptic esophagogastroscope. Likewise, an object far in the lung periphery of an adult may be more readily extracted with a flexible fiberoptic bronchoscope. In the patient with a radiopaque foreign body far in the lung periphery, simultaneous biplane fluoroscopy is a critical adjunct. The procedure is scheduled well in advance in the cardiac catheterization laboratory. Use of simultaneous biplane fluoroscopy in this setting is uniformly more successful than trying to use a mobile C-arm fluoroscope in the operating room.

MECHANICS OF EXTRACTION

SHARP POINTS

"Search not for the foreign body, but for the point of the foreign body" paraphrases the Jackson dictum crucial to the uncomplicated solution of these often challenging mechanical problems.[2] Long, pointed objects such as pins and needles are classified as either bendable or breakable. While it is often helpful to bend a pin during extraction, it is rarely desirable to break a pin or needle. The pin-bending forceps is designed specifically for this purpose and is most often used for extracting pins in the lung periphery (Fig 1). It proved invaluable in extracting a large earring with a post perforating the anterior pharyngeal wall (Fig 2).

Invariably, pins lodge point-upward, because the point lodges in the mucosal wall and the pin tumbles and then proceeds with the point trailing. The endoscopist's primary goal is to sheathe the point within the scope prior to removal. Usually, the object first must be grasped and moved distally to disengage the point. The scope is then advanced over the point, sheathing it within the tube.

The bronchoscope is aligned to approach the object in its long axis (Fig 3A). Here again, the biplane fluoroscope may be of assistance. Magnets also can be used in these situations. Tacks, nails, and large-headed foreign bodies in the tracheobronchial tree are released, sheathed, and removed with the inward rotation method[1] (Fig 3B).

Safety pins present difficult but fascinating mechanical problems for extraction. Fortunately, since the introduction of disposable diapers, they are infrequently encountered. Invariably, they are discovered to be open, since closed safety pins will pass

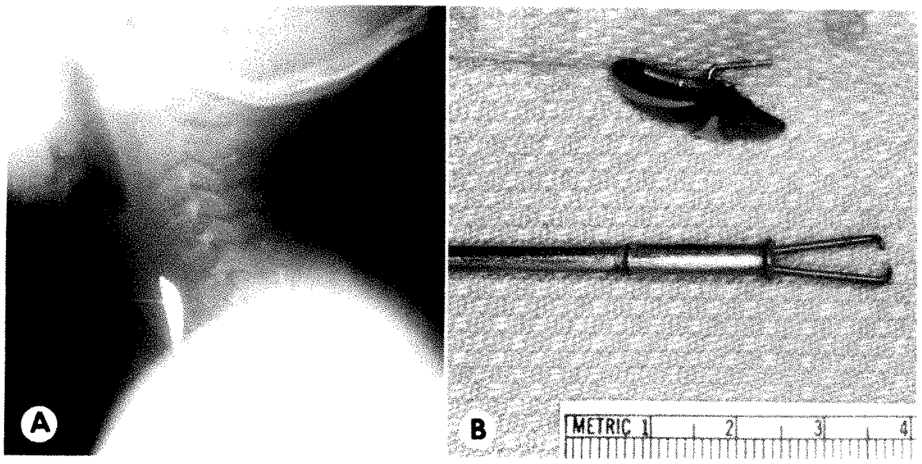

Fig 2. Earring lodged in cervical esophagus of 3-year-old girl. A) Lateral radiograph showing that sharp post protrudes anteriorly, creating potential hazard of additional trauma during extraction. B) After removal. Heavy reinforced tip of pin-bending forceps shown with earring and bent post. Post was bent to facilitate extraction so point trailed during withdrawal.

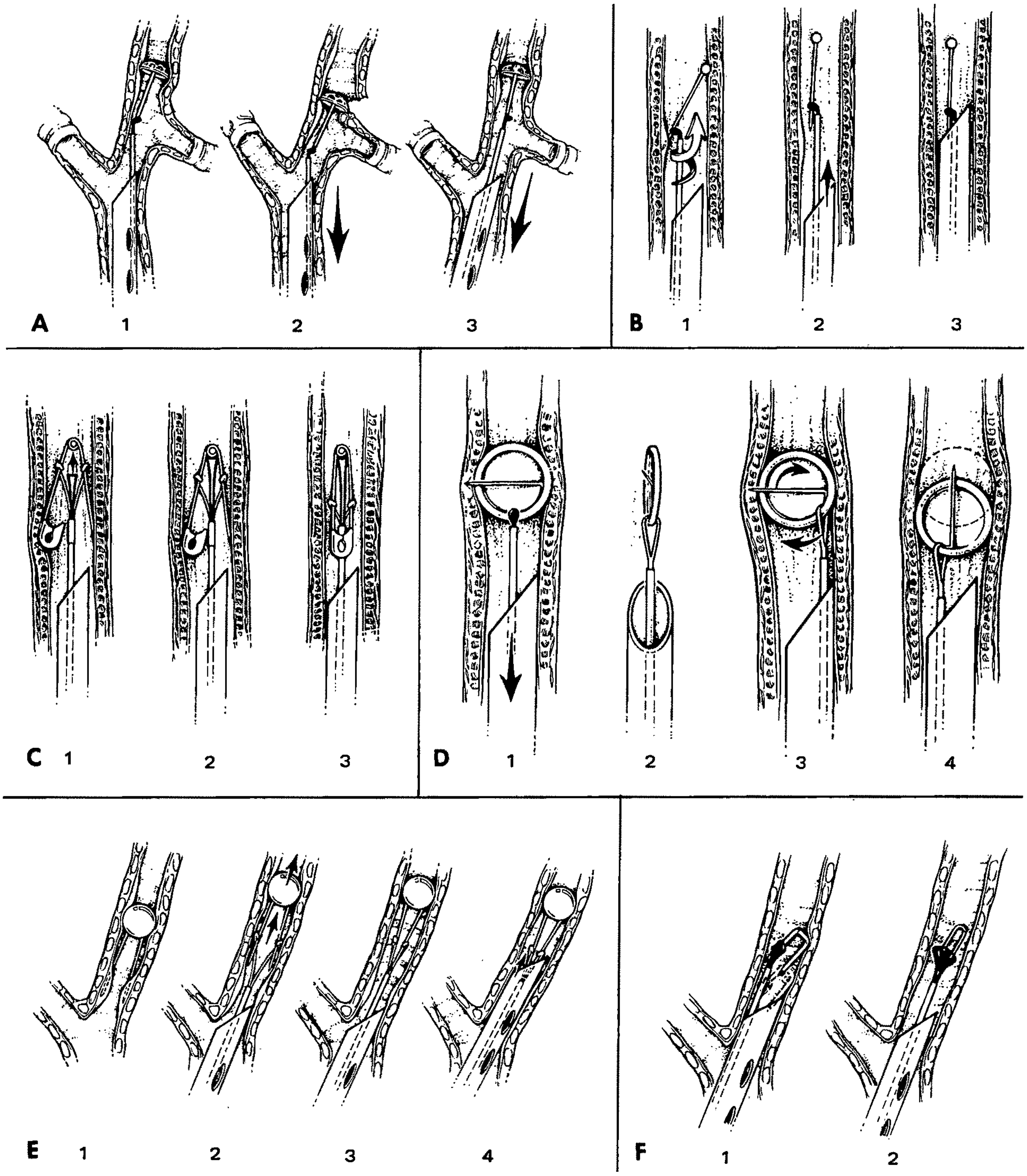

Fig 3. Techniques of endoscopic removal. A) Long axis traction is particularly important for pointed objects with large heads. Point may be easily located (1), but greater hazard lies in risk of tearing bronchial wall with head of tack (2). Positioning patient's head toward opposite side straightens axis of airway, permitting relatively safe, slow, steady withdrawal of object (3). B) Inward rotation method is used for pins or needles with imbedded point. Side-grasping forceps captures pin near point. Corkscrew motion is used to push pin distally while rotating it clockwise, freeing point and aligning shaft with long axis of forceps (1). Scope is advanced over point to sheathe it (2) for extraction (3). C) Clerf-Arrowsmith safety pin closer. Notched brace pushes spring away from blades (1), which simultaneously approximate point and keeper (2,3). Dangerous instrument. D) Rotation forceps. Forward-grasping forceps fix foreign body (1), increasing likelihood of laceration. Two pointed opposing blades of rotation forceps (2) permit foreign bodies with sharp points or jagged edges to rotate (3) so hazardous parts trail harmlessly during extraction (4). E) Technique of managing bendable double-pointed objects. Points buried in mucosal wall (1) are released by moving them proximally (toward center of patient) (2). Points are approximated (3), then sheathed for extraction by advancing rigid scope (4). F) Tucker staple forceps (1) is angled to permit sheathing of both points within beveled tip of bronchoscope. Jackson broad-staple forceps (2) grasps and protects both points during advancement of bronchoscope to sheathe them.

through the gastrointestinal tract. Open safety pins lodge point-up. Several mechanical alternatives are available for extraction.

Point-Sheathed Method. The point is sheathed within the tube while the smooth keeper slides up outside the scope.

Endogastric Straightening. The pin is advanced into the stomach with the keeper sheathed within the scope. A rotation forceps is then used to firmly pull the keeper up inside the tube, straightening the pin.

Gastric Version. Under fluoroscopic control a rotation forceps is used to grasp the spring. The pin is advanced into the stomach, reversed, then withdrawn with the point trailing.

Inward Rotation Method (Fig 3B).

Dangling Method. The keeper is held loosely with a rotation forceps, allowing the pin to turn crosswise. This method will work provided the length of the pointed branch is less than the lateral diameter of the esophagus.[2]

Clerf-Arrowsmith Safety Pin Closer (Fig 3C). This intriguing instrument is dangerous in the hands of the occasional operator. The pin may become tangled with the forceps, preventing extraction of the pin, forceps, or esophagoscope.

Pin buttons, such as campaign buttons, may be removed by using a rotation forceps (Fig 3D). Careful application of the two points allows the object to rotate, dangle, or tumble rather than being fixed against the mouth of the tube, increasing the likelihood of laceration. Thus, when a sharp edge exerts pressure against the mucosal wall, it rotates and dangles and is extracted with the point trailing.

Double-pointed objects pose special problems if both points cannot be sheathed within the lumen of the bronchoscope. Sometimes the two points can be converted to a single point and then sheathed (Fig 3E). This is possible with bendable types of double-pointed foreign bodies but not with tacks or staples. A staple forceps, a broad forceps (Fig 3F), or an endoscope with an expansile mechanism facilitates endoscopic retrieval of nonbendable double-pointed objects.

Partial dentures with (sharp) hooks intended to partially encircle adjacent teeth are particularly difficult to remove without severely lacerating the esophageal mucosa. Great care and patience are required: finesse, not force. Esophagotomy may ultimately be necessary.

SHARP, CUTTING EDGES

Bones lodged in the esophagus frequently have sharp points or edges. These are often cumbersome and difficult to sheathe within the esophagoscope. In this situation, a rotation forceps may be used.

Edges of aluminum pull tabs may be razor-sharp. They are rarely visible on plain radiography unless visualized directly end-on. Fluoroscopy cannot be used to aid extraction. A large-diameter endoscope is used to protect the mucosa from the sharp edges.

Razor blades pose similar problems. They are unlikely to pass through the gastrointestinal tract without perforation and require prompt surgical removal.

Glass is usually visible radiographically and in infants is most likely to originate from a broken food container.[3] Glass is most often associated with immediate perforation and mediastinal emphysema. An abscess may be a later complication. When an adult, however, gives a history or describes symptoms of supposed glass ingestion from a food container or food obtained in a restaurant, and no physical signs can be elicited, the physician must be extremely cautious. Every study should be carefully documented and all possible radiographic studies undertaken, because these cases invariably become medical-legal problems.

Broken parts of plastic toys constitute another type of foreign body that requires individual mention. These are extremely deceptive because they are not radiopaque.

POSTESOPHAGEAL FOREIGN BODIES

Most objects, including large or pointed ones, that pass into the stomach will traverse the entire gastrointestinal tract without complications. The child is merely given his regular diet without increasing intake of extra roughage. If normal bowel contents are allowed to carry the object along, the danger of obstruction or perforation is negligible. The position and progress of a pointed object is checked radiographically every 3 or 4 days until it passes. Parents are instructed to examine the stools but to return for immediate reevaluation should any symptoms of perforation or peritonitis develop.

If the foreign body remains in one position for more than 1 week, surgical removal may be considered. Foreign bodies that remain loose in the stomach for a long time are generally of little concern unless they are unusually large. However, lengthy objects that enter the stomach easily on their long axis have difficulty in passing through the duodedum in children under 2 years of age. Since they may cause perforation, endoscopic extraction is undertaken before they leave the stomach.

Needles swallowed by patients of any age, however, should be removed as soon as the diagnosis is confirmed by radiography. A needle perforating the stomach or intestine may cause minimal symptoms initially. However, at laparotomy, it may be found to be partially out of the bowel wall without signs of peritonitis. Needles tend to wander, later penetrating another viscus or major vessel. Abscess forma-

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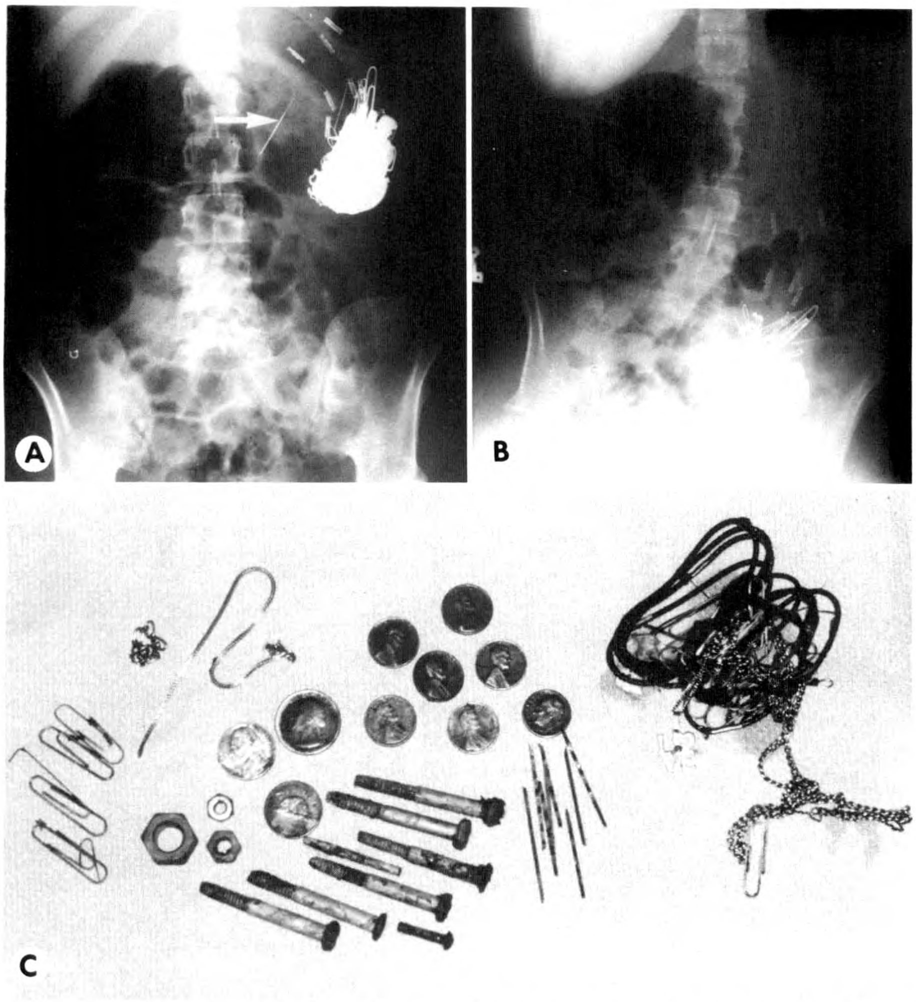

Fig 4. Patient with multiple gastric foreign bodies. A) Supine film of abdomen. Straight pin (arrow) is seen perforating wall of stomach. B) Upright film of abdomen. Weight of tangled mass of metallic foreign bodies pulls stomach into lower abdomen. C) Contents of stomach removed at laparotomy.

tion is another potential complication. Gastrotomy is not delayed if endoscopic removal is unsuccessful.

Figure 4 shows a sewing needle that migrated partway out of the stomach of an 18-year-old retarded girl who had multiple gastric foreign bodies. She had initially presented with a drawer-pull lodged in the cervical esophagus. The gastric foreign bodies were noted incidentally. Elective gastrotomy was planned for 3 weeks following endoscopic extraction of the drawer-pull, but symptoms of abdominal pain, vomiting, and low-grade fever dictated urgent laparotomy.

Finally, it is important to determine whether or not the patient's immunizations are up-to-date, since injury by a sharp contaminated object could lead to tetanus.

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Ann Otol Rhinol Laryngol 99:1990

TRACHEOBRONCHOPATHIA OSTEOCHONDROPLASTICA

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Tracheobronchopathia osteochondroplastica is an unusual disease of obscure causation characterized by cartilaginous or bony outgrowths into the lumen of the tracheobronchial tree. Our retrospective review of 15 patients, 8 of whom were women, revealed a mean age of 63.5 years. The most common symptoms were cough (66%), hemoptysis (60%), dyspnea on exertion (53%), and wheeze (30%). Thirteen percent of the patients were asymptomatic. Chest radiography was not helpful in the diagnosis. Tracheal tomography revealed typical beaded intraluminal calcification in 4 of the 12 patients tested. Mirror laryngoscopy initially revealed the abnormalities in 30% of the patients, and bronchoscopy confirmed the diagnosis and determined the extent of the disease in all patients. Even though upper airway involvement has been thought to be uncommon, 40% of our patients demonstrated abnormalities of the larynx and upper trachea. Histologic confirmation of heterotopic bone formation was obtained in 60% of the patients. Pulmonary function tests showed mild obstructive lung disease. There were no deaths directly attributable to the disease. Treatments attempted included cryotherapy, laser excision, external beam irradiation, and bronchoscopic removal of the obstructing lesions.

KEY WORDS — bronchoscopy, laryngoscopy, osteochondroplastica, osteoplastica, tracheal calcification, tracheal ossification, tracheobronchopathia, tracheopathia.

Tracheobronchopathia osteochondroplastica (TPO), also described by the term tracheopathia osteoplastica, is a peculiar disease of unknown cause. The characteristic feature of TPO is the presence of multiple ossified or cartilaginous sessile nodules in the submucosa of the trachea and bronchi.[1-6] Significant rigidity of the affected areas of the tracheobronchial tree contributes to the respiratory problems. These outgrowths originate from the cartilaginous structures (anterior and lateral walls) and hence spare the posterior membranous portion.[1-3] They vary in size and produce symptoms related to the luminal narrowing of the tracheobronchial tree, including the larynx and subglottic trachea. Bronchoscopy is usually diagnostic. The mucosa usually appears intact and normal.[2] The condition has been diagnosed at postmortem examination in the majority of cases.[2,7,8]

We recently encountered a patient who had severe subglottic narrowing caused by TPO. Most earlier reports do not mention the frequency with which this disorder affects the larynx, subglottic area, and upper trachea. The general understanding has been that TPO rarely affects the upper respiratory tract. Herein we describe and discuss our clinical experience in 15 patients with TPO and, in particular, assess the nature of upper airway involvement.

MATERIALS AND METHODS

We retrospectively reviewed the records of patients with the diagnosis of TPO made at Mayo Clinic and Mayo Medical Center from 1954 to the present. The records were obtained by computer search as well as review of the records of our tissue registry. Patients with calcification of tracheobronchial cartilage from other diseases were excluded. Cases with cartilaginous ossification and clinical evidence of projection of these outgrowths into the tracheobronchial lumen were included. Bronchoscopic documentation of TPO was also used as one of the criteria to be considered for this study. We analyzed the age, sex, underlying medical conditions, clinical features, pulmonary function data, radiographic aspects, findings from laryngoscopy and bronchoscopy, results of pathologic examination, treatments, complications, and outcome in these patients.

RESULTS

Our research revealed records of 15 patients with the unequivocal diagnosis of TPO. The mean age of the patients was 63.5 years, with a range of 23 to 81 years. Eight patients were women. A history of tobacco smoke inhalation was observed in 9 patients. The underlying active respiratory conditions at the time of diagnosis of TPO included chronic bronchitis in 10, reactive airway disease in 5, recurrent pneumonia in 3, and chronic sinusitis in 2 patients. Gastroesophageal reflux was noted in 2 patients and renal calculi were diagnosed in 2 patients. One patient had severe rheumatoid arthritis with possible pulmonary rheumatoid nodules, and another was found to have a large goiter that did not cause respiratory symptoms.

The main respiratory symptoms were cough (66%), mild degrees of hemoptysis (60%), dyspnea on exertion (53%), and wheeze (30%). Chest radiographs exhibited scattered areas of patchy fibrosis

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Presented at the meeting of the American Broncho-Esophagological Association, Palm Beach, Florida, May 2-3, 1990.

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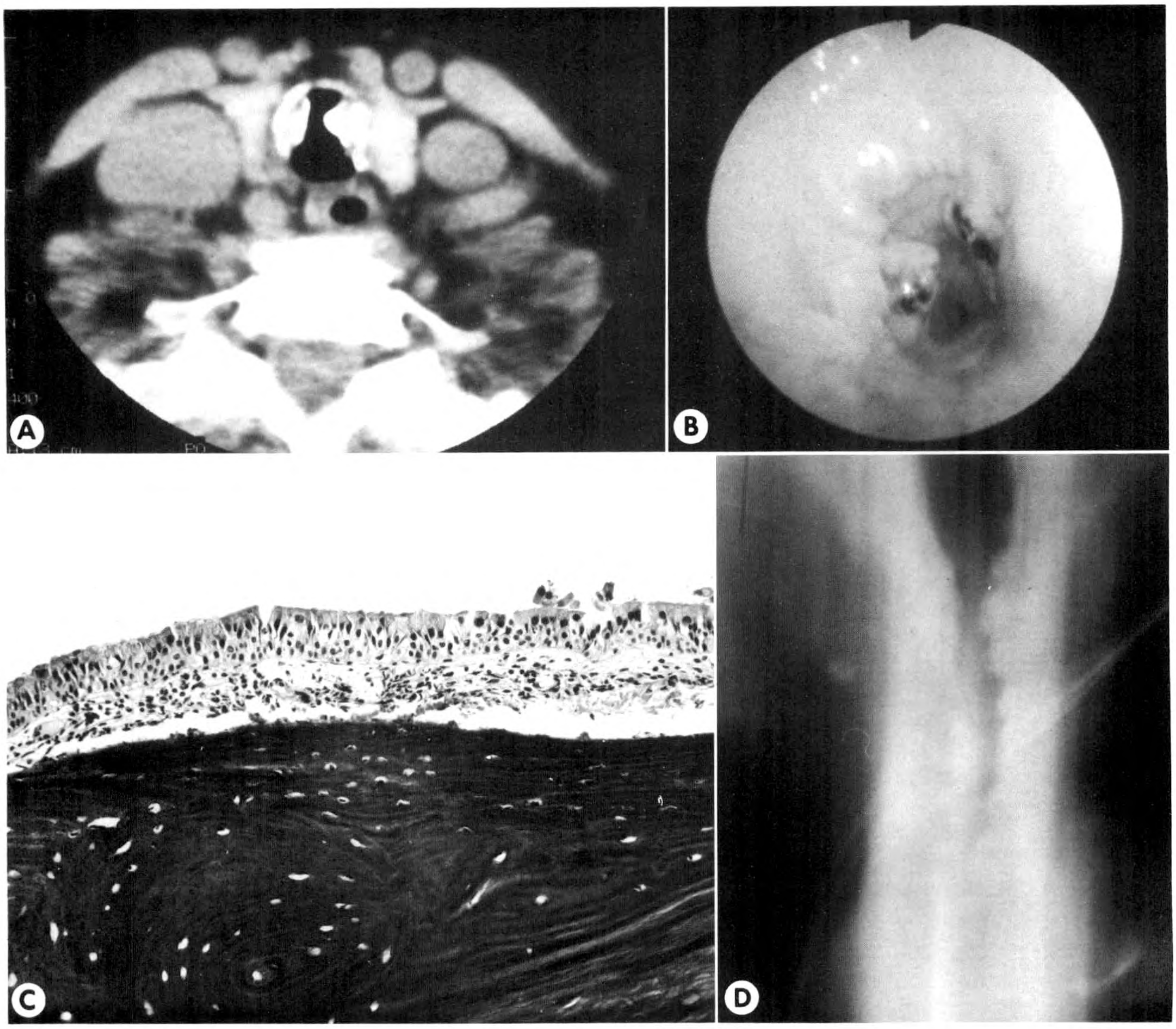

(Case 2) Tracheobronchopathia osteochondroplastica. A) Computed tomogram of upper trachea, disclosing projection of calcified nodules into tracheal lumen. B) Fiberoptic bronchoscopic appearance of disease in larynx, subglottic area, and upper trachea. C) Photomicrograph of lesion in upper trachea in patient demonstrating heterotopic bone formation with normal overlying respiratory epithelium (H & E, original x250). D) Anteroposterior tomogram of trachea demonstrating typical beaded appearance of left lateral wall of trachea.

in 5 (33%) patients, nonspecific pleural abnormalities in 3 (20%), nodular densities in 2 (13%), and lobar infiltrates in 1 (7%) patient. None of these abnormalities were thought to be related to TPO, although the patient with lobar infiltrate was considered to have developed postobstructive pneumonitis due to obstruction of lobar bronchi by TPO. Chest radiographs were normal in 5 (33%) patients. Tracheal tomography was obtained in 12 patients and typical beaded intraluminal calcification was demonstrated in only 4 (33%) patients. Narrowing of the tracheal lumen was described in 2 patients, and another patient was noted to have tracheal deviation. Tracheal tomograms showed normal findings in 5 (42%) patients. Computed tomography in 1 patient (case 2) revealed calcified nodules partially obstructing the tracheal lumen (see Figure, A). Pulmonary function tests were performed in 7 patients and the results suggested a mild obstructive pattern in 5 patients and mild extrathoracic airway narrowing in 1 patient. Lung functions were normal in the other patient.

The initial clinical diagnoses in several patients included asthma and bronchitis. When the medical management failed to relieve their respiratory symptoms, further diagnostic tests were undertaken. The diagnosis was made by laryngoscopy in 3 patients, whereas bronchoscopy confirmed the diagnosis and determined the extent of disease in all patients. Rigid bronchoscopy was performed in 14 patients, and 2 patients had both rigid and fiberoptic bronchoscopy. The disease involved both the trachea and bronchi in 6 (40%) patients, upper trachea alone in 6 (40%) patients, and the lower trachea in 1 patient. The typical findings included multiple nodular densities of various sizes compromising the tracheal lumen (see Figure, B). The membranous portion of the tracheobronchial walls was spared. The nodules felt hard and produced rigidity of the affected wall. Because of this rigidity, it was difficult to maneuver both the rigid and fiberoptic bronchoscopes through the diseased lumen. Mucosa overlying the nodules appeared normal, although in some patients there was some thinning of the mucosa. The troughs between the nodules were occasionally covered with thin mucoid and yellow mucus. Biopsies of the nodular projections into the trachea, performed on 11 patients, demonstrated normal respiratory epithelium in all cases except one, in which squamous metaplasia with hyperkeratosis was observed. Histologic analysis of the submucosal nodules revealed characteristic heterotopic bone formation (see Figure, C).

Treatment was considered only when the obstructive symptoms warranted. Various types of therapy attempted included laryngoscopic and bronchoscopic removal of nodules, cryotherapy, and application of a neodymium:yttrium aluminum garnet laser. The success of these procedures was varied, but generally the patients were noted to have improved respiratory status after treatment. There were no serious complications associated with treatment. There were no deaths directly attributable to the disease. The follow-up period of these patients averaged 9.4 years, with a range of 1.2 to 26 years. The following cases from our series document the upper tracheal involvement in TPO.

CASE REPORTS

Case 1. A 23-year-old man presented with a history of tracheal crusting suggestive of tracheal ozena. However, sinus radiographs were negative for chronic disease and findings on rhinologic examination were normal. The diagnosis of TPO was not established until laryngoscopy was performed. The diagnosis of TPO was made by laryngoscopy alone in this patient.

Case 2. A 73-year-old woman who was found many years earlier to be an asthmatic presented with inspiratory stridor, cough, streaky hemoptysis, and wheezing. Mirror laryngoscopy suggested subglottic obstruction. The diagnosis of TPO was confirmed at bronchoscopy (see Figure, B). The degree of subglottic narrowing was severe and more pronounced than the involvement of the distal trachea. Under general anesthesia, a rigid bronchoscope was passed into the upper trachea and the tracheal lumen gradually dilated with the rigid bronchoscope. We attempted ablation of the lesions with a neodymium:yttrium aluminum garnet laser, but only mucosal removal was accomplished. Charring of the ossified nodules was observed with no reduction in the size of the obstructing lesions. Several of the large nodular lesions were removed from the subglottic region with resultant improvement in respiratory status.

Case 3. A 71-year-old male smoker who presented to another institution with symptoms referable to the larynx and hemoptysis was clinically judged to have carcinoma of the larynx and received external beam radiotherapy on an empiric basis. The hemoptysis temporarily abated, only to recur 6 months later. He was seen at our institution and bronchoscopy revealed TPO.

Case 4. A 63-year-old female smoker who presented with a chronic productive cough and hemoptysis underwent rigid bronchoscopy with discovery of TPO in the entire trachea and right main stem bronchus extending to the bronchus intermedius. No distinct source of hemoptysis was identified. Cryotherapy was applied to a 5- to 6-mm lesion in the right distal trachea, with temperatures lowered to −65°C for a total of 6 minutes. The hemoptysis stopped, but recurred 14 months later. Repeat bronchoscopy noted no progression of lesions caused by TPO. The source of hemoptysis was not identified, but it was thought to arise from a large nodule near the bronchus intermedius.

DISCUSSION

Tracheobronchopathia osteochondroplastica, also known as tracheopathia osteoplastica, was first noted during a mirror laryngoscopy by von Schroetter in 1896, according to Muckleston.[9] Wilks,[10] however, provided the first microscopic description in 1857. Detailed postmortem descriptions are credited to Rokitansky in 1855 (according to Dalgaard[7]) and Luschka in 1856 (according to Moersch et al[11]). Dalgaard[7] reported that there were 90 cases described in the literature by 1947. Martin[2] found 245 cases as of 1974. That the diagnosis of TPO is rarely considered is because of a lack of awareness of this entity, rather than the reported rare occurrence.[12,13] Jepsen and Sorensen[14] noted that TPO was detected in 5 of 3,500 bronchoscopies, whereas Eimind[15] observed no cases of TPO among 25,000 bronchoscopies. A majority of the nearly 300 cases described so far were discovered at autopsy, although more recent publications reveal many antemortem diagnoses.[3,4,6,8,16] Of the 26 cases reviewed by Martin,[2] 15 were diagnosed at autopsy, 5 after surgical procedures, and 6 following bronchoscopy. Secrest and colleagues[5] estimated that only 5% of the cases are diagnosed during life. However, we and other authors[8] believe that it occurs more commonly than reported. It is not recognized more often because of its indolent and asymptomatic nature and because of the relative lack of awareness among clinicians of this entity. It is not uncommon to see minor degrees of TPO during bronchoscopy. Such lesions have been described as "minimal lesions."[17] Our report updates an earlier publication of three cases from our institution[1] and spans a 35-year period. The mean age of our patients was 63.5 years, similar to the mean age in other studies despite the fact that this study was not a postmortem review. Our findings support the conclusion that this process is primarily diagnosed in older adults.[3,7,16] However, the youngest patient in our series was 23 years old at the time of diagnosis. The youngest known patient was a 12-year-old described by Härmä and Suurkari.[3] It is also conceivable that the disease process may begin at an earlier age and that because of its slow progression symptoms may not appear until later in life. Once thought to more commonly affect males, TPO seems to occur with equal frequency in males and females, as observed by us and others.[3,7]

The clinical presentation of TPO is generally related to the degree of airway obstruction, whether it is at the glottic, subglottic, or bronchial level.[6] However, the actual morbidity and mortality caused by TPO are difficult to determine, because the majority of cases defy clinical recognition during life. Even if symptoms are present, most cases are diagnosed as asthma or bronchitis. Among our patients, 10 had the earlier diagnosis of bronchitis or asthma. Occasionally, the diagnosis has been made after unexpected difficulty during endotracheal intubation for anesthesia.[18] In any patient with upper airway noises, wheeze, and stridor, one should consider TPO in the differential diagnosis. Hemoptysis may result from the rubbing of one nodule against another in the tracheobronchial tree. In one of our patients, an ulcer was noted in the area of contact between two opposing nodules in the trachea. Lobar or segmental collapse may result when the outgrowths obstruct the bronchial lumen. Postobstructive pneumonitis as a result of this phenomenon was observed in one of our patients.

The cause and pathogenesis of TPO are unknown. Many etiologic factors have been proposed. Wilks[10] suggested that chronic infection was responsible. Ribbert[19] postulated that TPO develops as a result of a congenital anomaly. Jepsen and Sorensen[14] thought that chemical or mechanical irritation caused TPO. A degenerative basis for the disease was considered by Hiebaum.[20] Hempel and Gläser[21] postulated a metabolic basis. Although two of our patients had nephrolithiasis, we believe it was coincidental and unrelated to their TPO. Dalgaard[7] suggested that there may be an underlying congenital predisposition to the development of TPO. In this regard, we recently reported a familial occurrence of TPO in a female and her biologic mother.[22] Vaheri and Vaheri[23] stated that a chronic, slowly advancing inflammatory process may be responsible for TPO. Some authors have suggested that TPO is related to end-stage primary amyloidosis.[24-26] Special stains for amyloid were negative in several of our patients. Compared to the number of patients with amyloidosis seen in clinical practice, the number of cases of TPO is very small. All 245 cases of TPO reviewed and reported by Martin[2] in 1974 were without amyloidosis, and among the 30 cases of all other forms of respiratory tract amyloidosis reported in the same year, there was no case of TPO.[27] Thus, it is unlikely that TPO is the end result of amyloidosis. Currently, however, three etiologic theories predominate: 1) that the disease stems from abnormalities in the tracheal elastic tissue, as Aschoff-Freiburg[28] postulated; 2) that along with this process, as Dalgaard[7] stated, the elastic tissue undergoes metaplasia to elastic cartilage that subsequently ossifies; and 3) that as Virchow[29] explained, the nodular excrescences represent exostoses and ecchondroses from the cartilaginous trachea, which then ossify. Suffice it to state that the exact molecular basis of TPO remains unknown.

Biopsy of TPO lesions can be challenging because of the bony nature of the lesions and the limitations of working through the bronchoscope. Reports comment on the difficulty of obtaining adequate tissue via the flexible fiberoptic bronchoscope,[2] but with selection of smaller nodules this maneuver can be accomplished, as was done in our cases. Nevertheless, larger biopsy forceps used through a rigid bronchoscope are more likely to yield adequate specimens. Histologically (see Figure, C), the overlying mucosa is typically normal, with inflammatory debris and cartilage or bone appearing in the submucosa. Of interest, hemopoietic fatty marrow is often present and is encased by bone.[30]

Routine chest radiography is usually nondiagnostic in TPO, although an occasional case has been diagnosed.[31] We believe that the nonspecific chest x-ray findings among our patients were unrelated to TPO. Tomography of the trachea is useful in documenting the characteristic intraluminal nodular lesions with the beaded or scalloped appearance of the tracheal wall.[32,33] However, in only four of our patients were the characteristic lesions noted (see Figure, D). The variable size of the nodular lesions and the variable degree of calcification may cause difficulty in seeing the lesions on the tomogram.[31,33] Also, TPO should be distinguished from cartilaginous calcification and ossifications caused by paratracheal lymph nodes, hamartomas, chondrosarcomas, papillomas, and other neoplasms.[34,35] Computed tomography has been used to document TPO.[35-37] The multiple submucosal nodules and plaques that involve the trachea can be well demonstrated by this technique.[35] Repeat computed tomography of the affected tracheal segments in one of our patients did show an improved airway lumen following rigid bronchoscopic dilation. Computed tomography therefore may also aid in determining the progression of the disease, which has been somewhat difficult to quantitate with flow-volume loops or bronchoscopy.[38] Pulmonary functions tests in seven of our patients showed a mild obstructive pattern, similar to earlier observations.[16] Flow-volume loops have been used to document the degree of major airway obstruction in patients with TPO.[39] Our patient who underwent bronchoscopic treatment of

TPO noted significant improvement in her respiratory symptoms, but the flow-volume loop did not differ significantly from the preoperative findings that showed both mild inspiratory and expiratory airway obstruction.

The bronchoscopic appearance of TPO is quite characteristic (see Figure, B). The first bronchoscopic description of TPO was by Killian[40] in 1897. The literature abounds with descriptions such as those of a veritable mountainscape,[7] a rock garden,[41] a stalactite cave,[25] and a cobble-stoned appearance.[2] A gritty, grating sensation is palpable when the rigid bronchoscope is passed over these lesions. All of our patients were confirmed by bronchoscopy to have TPO, although a significant number (30%) of cases were observed first with mirror laryngoscopy.

Most frequently, TPO is reported to involve the lower two thirds of the trachea, and it often involves the proximal portions of the major bronchi.[2] In nearly 80% of our patients, the disease process was more extensive in the trachea than in the bronchi. However, exclusive bronchial involvement, found in one of our patients, does occur,[16] and TPO should be included in the differential diagnosis of endobronchial lesions. The presentation of TPO can be similar to that of bronchogenic carcinoma, and although the bronchoscopic appearance is said to be diagnostic, even experienced bronchoscopists may misdiagnose this condition.[42] The fact that one patient in this series underwent a course of external beam irradiation outside our institution because the TPO was thought to be bronchogenic carcinoma emphasizes this point.

Laryngeal involvement has been reported only occasionally,[8] and TPO rarely affects the larynx exclusively.[43] At least one case of difficult intubation secondary to TPO has been noted in the literature.[18] Paaske and Tang[43] encountered a patient with TPO localized to the larynx who presented with symptoms of progressive dyspnea and dysphagia that necessitated tracheotomy. Subsequently, the patient underwent partial resection of the osteoplastic tissue from the postcricoid region. The treatment included removal of a cricoarytenoid joint that was fixed by spongy bone. It is not mentioned if the patient was decannulated after this intervention, but the patient's dysphagia improved. Subglottic and tracheal TPO producing stridor occurs infrequently but can contribute to fatality.[25] Hirsch and colleagues[35] described a treatment using an anterior fissure technique to treat symptomatic narrowing of the subglottis and high trachea by removing the obstructing lesions, covering areas denuded of mucosa with periosteum taken from the clavicle, and placing a Silastic stent for support. Initially the symptoms resolved, but they recurred 3 months later and the patient had to undergo tracheotomy. Resection of seven tracheal rings for stenosis secondary to TPO has been reported to be successful.[44] One patient in the present series presented with stridor and wheezing secondary to high tracheal obstruction. The symptoms greatly resolved after forceps removal of obstructing lesions through the rigid bronchoscope. Six months after this intervention the patient is doing well. Certainly, endobronchial TPO lesions can produce recurrent pulmonary infections[1] (20% of patients in this series) that are occasionally refractory to medical management.[26] We advocate conservative endoscopic removal of obstructing lesions with sparing of as much mucosa as possible in cases of airway obstruction. Open procedures should be reserved for instances in which this treatment fails.

Although hemoptysis often precedes the discovery of TPO, no site of bleeding is found in the majority of patients, and the cause and effect relationship is unclear. External beam irradiation has been used to control hemoptysis in one case of TPO.[45] One of our patients who underwent external beam irradiation for presumed laryngeal carcinoma did notice disappearance of hemoptysis for 6 months. However, it is very unlikely that radiotherapy is totally effective in TPO. Such descriptions as ours (case 4) of cryotherapy to treat TPO in one patient with hemoptysis have not been reported before. Repeat bronchoscopy 14 months later, when hemoptysis recurred, revealed no progression of the disease.

In conclusion, TPO is an unusual entity of unclear cause in which heterotopic ossification of laryngotracheobronchial cartilages can produce symptoms directly related to the location and degree of airway obstruction. Whereas previously this condition was diagnosed most frequently at autopsy, the technology of flexible fiberoptic bronchoscopes and laryngoscopes has made the tracheobronchial tree more accessible, and hence most cases of TPO should be amenable to clinical diagnosis. The clinician should include TPO in the list of differential diagnoses when confronted with symptoms suggestive of diseases of the upper airways and the tracheobronchial tree.

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ADDENDUM

Since this manuscript was submitted, we have seen two additional patients with TPO. The first patient was an 80-year-old man who presented with a history of pneumonia and difficulty in expectorating sputum. He had undergone several neodymium:yttrium aluminum garnet laser treatments for "tracheal stricture." Bronchoscopy at our institution established moderate airway narrowing due to TPO involving the proximal and middle trachea. The second patient was a 61-year-old man with persistent cough and culture of sputum exhibiting growth of *Pseudomonas aeruginosa*. He too was diagnosed as having tracheal stricture, and because of the failure of carbon dioxide laser therapy, he was referred to our institution. Bronchoscopy revealed changes characteristic of TPO in the subglottic area, the entire length of the trachea, and the proximal main stem bronchi. Since both patients were judged to be minimally symptomatic, continued observation and symptomatic treatment were recommended. These cases again demonstrate the lack of awareness of this entity among physicians and the poor response of the disease to laser treatment.

Ann Otol Rhinol Laryngol 99:1990

BRONCHIAL FOREIGN BODIES: AN UNCOMMON WAY OF ENTRY

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The author describes two cases of bronchial foreign bodies that were not inhaled. One of them was found in the right lower bronchus after having penetrated through a wound in the chest wall. The other was lodged in the right main bronchus after penetration through a wound in the soft tissue of the neck. Both foreign bodies were successfully removed with the bronchoscope.

KEY WORDS — bronchial foreign bodies, bronchoscopy, penetrating wound.

Foreign bodies of the lower airways are not very common as a disease entity. However, with regard to the pulmonary complications so often produced by them, they constitute an important chapter in pulmonary pathology, particularly in children.

Nearly all foreign bodies in the airways are inhaled. However, the increase in violence and crime in large cities has made it possible for us to see cases in which the chest wall or the soft tissues of the neck are perforated by bullets, fragments of shells, or other metallic objects. I know of only two case reports in which the foreign bodies were removed endoscopically after having penetrated the airways through the chest wall or the soft tissues of the neck.[1,2]

Jackson and Jackson[1] mentioned that foreign bodies, especially metallic ones, can reach the bronchi by penetration of the chest wall. They referred to a case in which a bullet was removed with a bronchoscope.

Bryant[2] reported the case of a patient who was struck in the neck by a fragment of a sledgehammer. Radiographs showed a metallic foreign body in the left lower bronchus that was successfully removed through the bronchoscope. In the same report Bryant also made reference to personal communications of four other cases from C. Norris and P. Holinger.

In the present report I describe two other cases of foreign bodies that had an uncommon way of entry.

CASE REPORTS

Case 1. In January 1984 a 35-year-old man was brought to an emergency hospital because of a

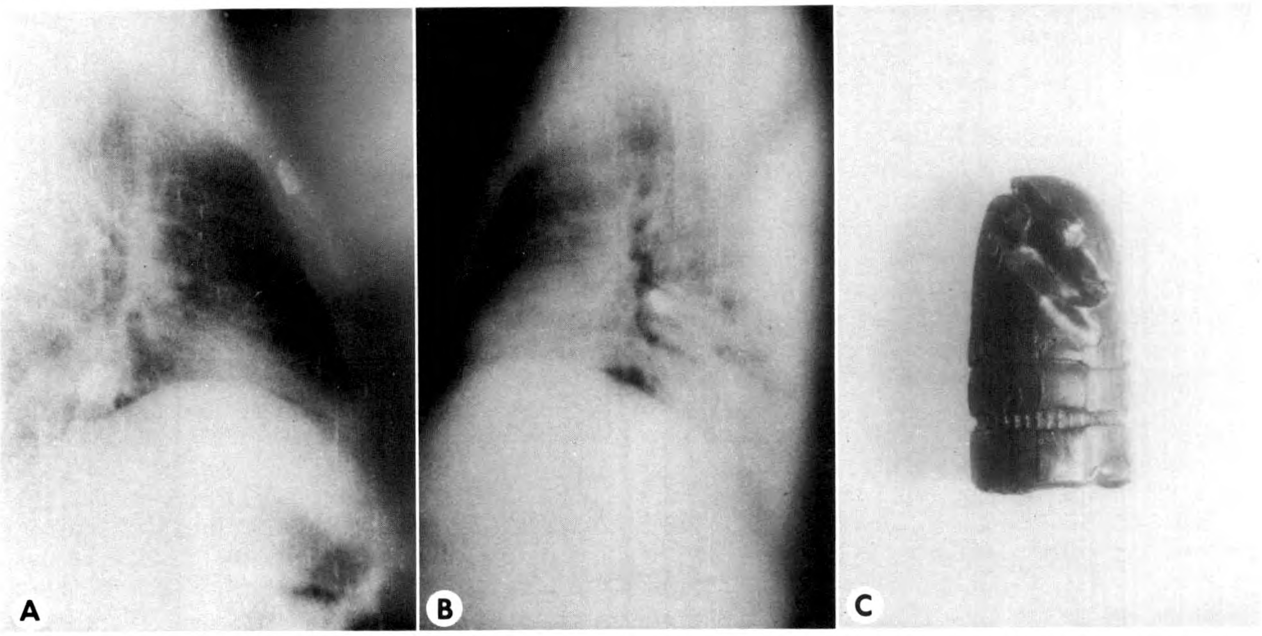

Fig 1. (Case 1) A) One foreign body is in right lower lobe of lung. Second foreign body is in sternum. B) Foreign body is in lower right bronchus. C) Removed foreign body (bullet).

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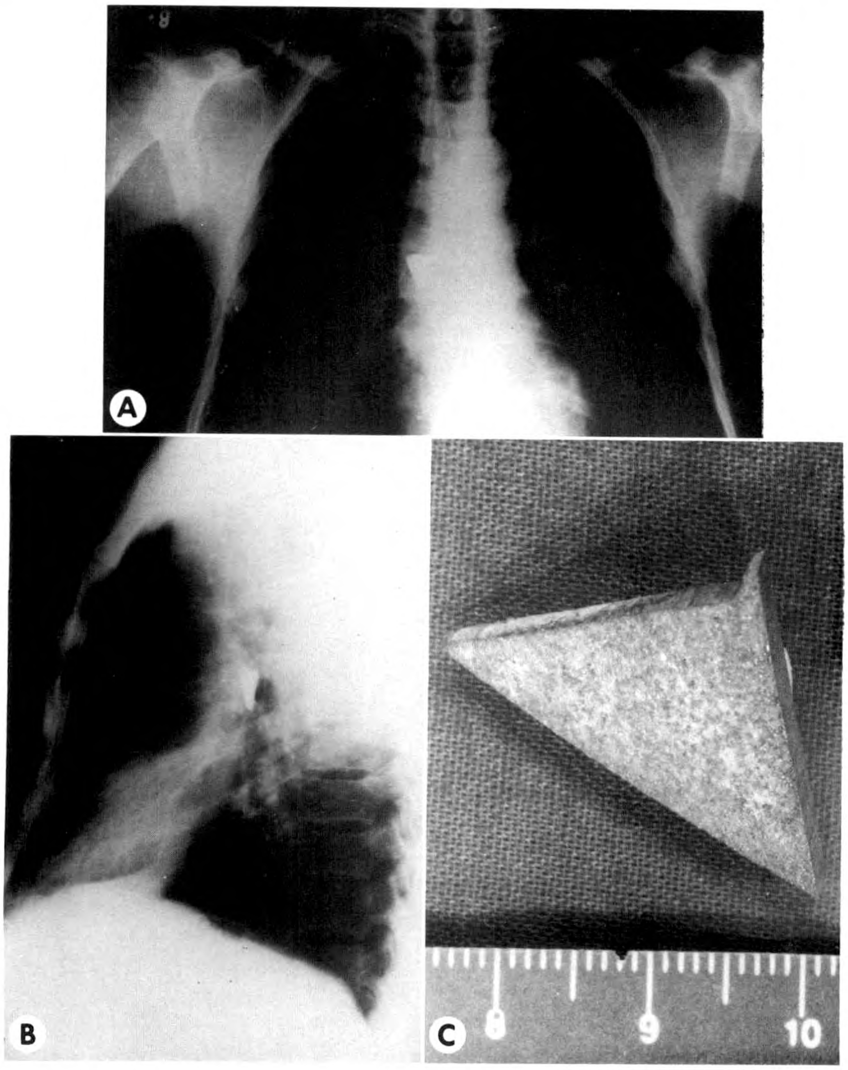

Fig 2. (Case 2) A) Posteroanterior view of metallic foreign body in right main bronchus. B) Lateral view of metallic foreign body in right main bronchus. C) Removed foreign body (fragment of circular saw).

street fight. He had been shot twice in the chest and was semicomatose with two penetrating wounds, one in the sternum and the other in the lower anterior wall of the right chest. Radiography performed in the emergency room showed a metallic foreign body (a bullet) in the right lung near the diaphragm (Fig 1). A second bullet was lodged in the sternum. The bullet in the sternum was surgically removed, and 5 days later the patient was discharged with the recommendation to return for further observation. Four days after his discharge from the hospital he suddenly developed a spasmodic cough resistant to sedation. Upon returning to the hospital he was referred to our clinic and was subjected to a new x-ray study of the chest. Comparison with the radiographs taken at the emergency hospital showed that the bullet had apparently moved up and was in the lower right bronchus. One possibility is that the bullet eroded into the lower right bronchus and moved up because of the strong cough. Under topical anesthesia and slight sedation a bronchoscopy was performed. The mucosa of the right bronchus was congested and free of secretion, and the foreign body was seen at the entrance of the right lower bronchus. With a large forward-grasping forceps it was removed along with the tube. The following day the patient was discharged without symptoms.

Case 2. In May 1986 a 45-year-old man was working in a sawmill with a large circular saw when he was struck in the neck and fell. He had a sharp pain in the neck and saw some bleeding. Brought to an emergency hospital, he was examined. A small wound, similar to an incision, was seen in front of his neck just below the cricoid. The wound was cleaned and sutured, and the patient was sent home. The next day he developed a cough with bloody sputum. On returning to the hospital he was referred to our clinic, and an x-ray study of the neck and chest was performed. No abnormalities were found in the neck x-ray and there was no sign of emphysema. However, the chest x-ray showed a metallic foreign body at the entrance of the main right bronchus (Fig 2). Apparently the sharp metallic object, projected with great force, had perforated the thin soft tissues of the neck in front of the cervical trachea, then the trachea itself, and then fallen into the airway. Bronchoscopy was performed under topical anesthesia and sedation. The patient had a small elevation in the anterior wall of the trachea, just below the larynx, with a blood clot in it. The foreign body was identified in the right main bronchus. With a rotation forceps it was removed with the bronchoscope. The next day the patient was discharged without any symptoms.

Comment. The cases described here call attention to the fact that metallic objects can be localized in the airways whenever they penetrate the chest wall or the soft tissues of the neck. Depending upon their location, these foreign bodies may be removed endoscopically. A thorough examination must be performed, especially with radiography.

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SIXTH BIANNUAL OTOLARYNGOLOGY–HEAD AND NECK SURGERY SEMINAR

The Sixth Biannual Otolaryngology–Head and Neck Surgery Seminar will be held October 27, 1990, at the Mayo Clinic Scottsdale in Scottsdale, Arizona. The seminar will be directed by Lawrence W. DeSanto, MD. For further information, contact Trish Gean, Mayo Clinic Scottsdale, 13400 East Shea Blvd, Scottsdale, AZ 85259; (602) 391-8300.

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THE DEAFNESS RESEARCH FOUNDATION OTOLOGICAL RESEARCH FELLOWSHIP FOR THIRD YEAR MEDICAL STUDENTS

The Deafness Research Foundation's Otological Research Fellowship will be sponsored by a department of otolaryngology conducting otological research. Where a unique opportunity exists in a related discipline, the fellowship may be conducted in that discipline while maintaining liaison with the department of otolaryngology. The fellowship would be scheduled as a one-year block of time at the end of the third year of medical school, thus requiring a one-year leave of absence from the medical school curriculum. Applications for 1991 must be received by November 15, 1990. For more information, please contact Walter A. Petryshyn, MD, Medical Director, The Deafness Research Foundation, 9 East 38th Street, New York, NY 10016; (212) 684-6556.

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VASCULAR INJURY FOLLOWING FOREIGN BODY PERFORATION OF THE ESOPHAGUS

REVIEW OF THE LITERATURE AND REPORT OF A CASE

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Esophageal perforation resulting from foreign body ingestion is a rare occurrence. Most of the complications associated with this event, such as retroesophageal abscess, mediastinitis, pericarditis, pneumothorax, and pneumomediastinum, are widely recognized. However, little attention has been directed to the possibility of vascular injury caused by the perforating object. Isolated case reports have described significant morbidity and mortality subsequent to major vascular trauma resulting from an esophageal foreign body, usually emphasizing the presence of a "signal" hemorrhage from the gastrointestinal tract as a key to diagnosis. This report describes a case of esophageal perforation caused by an ingested fishbone that resulted in significant aerodigestive hemorrhage, possibly as the result of an unusual isolated vascular injury. The literature on vascular trauma following foreign body perforation of the esophagus is reviewed, and suggestions for the diagnosis and treatment of these dreaded complications are made.

KEY WORDS — esophageal perforation, foreign body ingestion, vascular injury.

INTRODUCTION

Whether the result of instrumentation, tumor, spontaneous rupture, trauma, or foreign body ingestion, esophageal perforation is an event associated with significant morbidity and mortality. The incidence of perforation following foreign body ingestion appears low; however, the complications are no less severe.[1] Paraesophageal and retroesophageal abscess, mediastinitis, pericarditis, pneumothorax, pyopneumothorax, and pneumomediastinum are all well-described sequelae of esophageal perforation by an ingested foreign body.[1-5] Surprisingly, little attention in the literature has been directed to the possibility of vascular injury caused by the perforating object. A fistula developing between the esophagus and a major vessel in the neck or mediastinum has been described in various reports, with few patients surviving this unusual and catastrophic event.[1,6-11] This report describes a case of esophageal perforation subsequent to ingestion of a fishbone that resulted in significant aerodigestive hemorrhage, possibly caused by an unusual isolated vascular injury. The literature on vascular trauma following foreign body perforation of the esophagus is reviewed, and diagnostic and therapeutic options are discussed.

CASE REPORT

A 44-year-old man was seen at the University of Virginia Health Sciences Center Department of Otolaryngology–Head and Neck Surgery for hemoptysis that had started abruptly 6 hours before his arrival at the hospital. Five days prior to his hospital admission, while vacationing in Mexico, the patient developed odynophagia and a foreign body sensation in his throat while eating fish for dinner. He thought that he had swallowed a fishbone and sought medical treatment from a local physician, who prescribed 1 day of penicillin therapy without further evaluation. Although the foreign body sensation resolved over the ensuing 48 hours, the odynophagia persisted.

On examination the patient had bright red hemoptysis with no stridor or dyspnea. Flexible fiberoptic laryngoscopy revealed active bleeding from the cervical esophagus with reflux into the laryngeal introitus. No foreign body or mucosal tear was evident. There was no fluctuance or crepitance of the cervical soft tissues, and the patient was afebrile. A barium swallow study showed no extravasation of contrast medium from the pharynx or esophagus. Fluoroscopy of the neck did reveal a radiopaque linear object with a surrounding lucent area in the retroesophageal soft tissue (Fig 1). Rigid esophagoscopy was performed with general endotracheal anesthesia. Following removal of a large amount of clotted blood from the cervical esophagus, a foreign body was identified protruding from the midline of the posterior wall of the esophagus at approximately 20 cm from the central incisors. The foreign body was removed with grasping forceps and identified as a fishbone (Fig 2). No purulent drainage or hemorrhage was present from the site of the esophageal perforation after removal of the fishbone.

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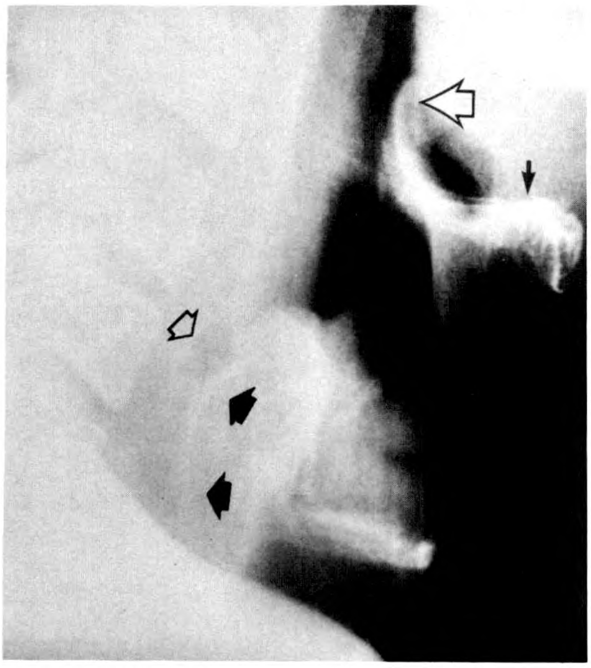

Fig 1. Lateral radiograph of neck demonstrating linear radiopaque foreign body (large filled arrows) with surrounding radiolucent area at superior tip (small open arrow) located in esophageal soft tissue. Large open arrow — tip of epiglottis, small filled arrow — hyoid bone (anteriorly).

The patient was admitted to the hospital and treated with intravenous penicillin G procaine and restricted from oral intake. Twenty-four hours after endoscopy he was allowed a clear liquid diet, with no hemorrhage, fever, or subcutaneous emphysema developing. He was discharged home on a regimen of oral penicillin, and has had no problems after 12 months.

DISCUSSION

The ingestion of foreign bodies is not an unusual event. Certain groups, such as children, people with psychoses or altered mental status, prisoners, and denture wearers, exhibit a greater propensity toward swallowing indigestible objects.[2] Bones, coins, pins, and dentures are some of the more commonly ingested foreign bodies, but others have been described.[1] Impaction of the object in the esophageal lumen is common and is often related to external compression or intraluminal narrowing of the esophagus or factors that affect its neuromuscular function. Three sites of anatomic narrowing — the cricopharyngeus, the diaphragmatic end of the esophagus, and the area of the aortic indentation — also have a predilection for foreign body obstruction.[11] Once impacted, the chance of spontaneous passage is unlikely as mucosal edema secondary to local trauma develops.[1]

Esophageal perforation resulting from foreign body ingestion is rare, with the incidence reported to be between 1% and 4%.[1,5,6] Impaction of the offending object with transmural inflammation and pressure necrosis of the esophageal wall seems to precede the penetration of the foreign body in many cases. That the majority of perforations occur after 24 hours of impaction in the esophagus would seem to support this concept.[1] The inflammatory and cardiopulmonary complications associated with foreign body perforation of the esophagus, such as retroesophageal and paraesophageal abscess, mediastinitis, pericarditis, pneumothorax, pyopneumothorax, and pneumomediastinum, have been thoroughly described in regard to their symptomatology, diagnosis, and treatment.[1-5,12,13] Vascular injury following foreign body perforation is a complication that has not been as well recognized, but is no less significant for its associated morbidity and mortality.

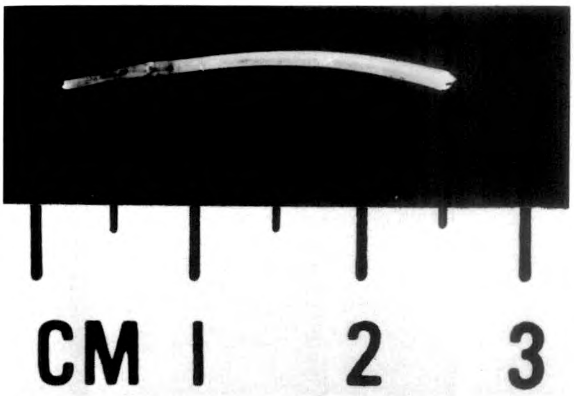

Fig 2. Fishbone removed from posterior wall of esophagus at time of endoscopy.

Esophagoaortic fistulas resulting from foreign body perforation of the esophagus account for the vast majority of vascular complications reported in the literature.[1,9,10] To date, 86 cases of aortic injury from an ingested object have been reported, with none of these patients surviving.[1] Most of these fistulas are caused by sharp foreign bodies such as bones, pins, or wires, with the majority occurring in the thoracic esophagus at the region of the aortic indentation.[9,10] However, coins have also been reported to have eroded through the esophagus and aorta with equally disastrous results.[9,10] A review of 82 cases by Sloop and Thompson[9] described the characteristic clinical features found in patients with an esophagoaortic fistula. In most cases, the final exsanguinating hemorrhage is preceded by a small "signal hemorrhage" presenting as hematemesis or hematochezia. This initial signal bleed is usually bright red, or arterial, in nature, suggesting hemorrhage from an arterial trunk. Recognition of this event has great diagnostic significance as it usually occurs hours to days before exsanguination, thus providing an opportunity to institute treatment. Although the mortality has been 100%, Sloop and Thompson did report that they were able to effect a repair of the esophagoaortic fistula in one patient who subsequently died of respiratory failure on the second postoperative day.

Other reports have described more unusual complications involving major arteries in the neck. Two cases of fistulous communication between the esophagus and the common carotid artery have appeared in the literature.[6,11] In one report, ingestion of a chicken bone resulted in perforation of the right lateral cervical esophagus and right common carotid artery with immediate massive arterial hematemesis and death.[6] A second case has been described, in which a left common carotid artery false aneurysm developed 1 week following ingestion of a fishbone that perforated the cervical esophagus.[11] In this patient, a lateral radiograph of the neck 2 days after ingestion of the foreign body demonstrated a radiopaque object and soft tissue swelling, which was treated with antibiotics and observation. When the patient developed hematemesis 7 days after swallowing the fishbone, an arteriogram was obtained that demonstrated the false aneurysm. This patient survived the vascular complication, which was treated with excision and ligation of the common carotid artery and repair of the esophageal fistula. In a third report describing injury to a cervical vessel, a fistula from the esophagus to the left lingual artery occurred after ingestion of a chicken bone, with prompt treatment resulting in the patient's survival.[8] This patient's case was unusual in that her bleeding presented as melanic stool 1 week after she ingested the bone, with recurrent bleeding 3 days later from the lower gastrointestinal tract. Rigid esophagoscopy disclosed a cervical esophageal perforation with active bleeding, which was controlled by intravenous vasopressin with ligation of the left lingual artery and repair of the esophageal fistula.

Vascular structures other than the aorta may be at risk for injury when a foreign body perforates the thoracic esophagus. A communication from the esophagus to the azygous vein has been reported following a chicken bone perforation of the right posterior esophageal wall.[7] This injury resulted in a suppurative thrombophlebitis of the azygous vein, with sepsis and progressive respiratory failure resulting in the patient's death despite antibiotic and supportive therapy. This unusual vascular complication was identified at autopsy examination; however, no foreign body was found at autopsy or during an esophagoscopy performed prior to the patient's death. The author postulated that the bone had temporarily perforated the esophagus and azygous vein before being dislodged by the antiperistalsis of retching. The anatomy of the mediastinum further supports the possibility of this complication, as the azygous vein is in contact with the right posterior surface of the esophagus from the level of the right bronchus inferiorly for a distance of five thoracic vertebrae.[7]

The present case of esophageal perforation following ingestion of a fishbone is similar in many respects to the previously published reports, but was unique in presentation and what appears to be the vascular injury. As with most of the reported cases, our patient experienced initial pain on swallowing along with the sensation of a foreign body being present, followed by persistent odynophagia. In the present case, the initial aerodigestive signal hemorrhage presented as hemoptysis, rather than hematemesis, melena, or hematochezia as has been previously reported. Although examination revealed the source of bleeding to be the esophagus, the striking bright red hemoptysis made laryngeal or tracheobronchial disease the initial etiologic consideration. This fact emphasizes that any aerodigestive hemorrhage may be the diagnostic "signal" bleed, alerting the clinician to the possibility of foreign body injury to vascular structures.

The source of bleeding in our patient is somewhat perplexing. On the basis of the location of the perforating fishbone in the midline of the posterior wall of the esophagus, distal to the cricopharyngeus and proximal to the aortic indentation, we propose that submucosal injury to one of the arterial branches of the esophagus occurred. The arterial supply to the cervical and proximal thoracic esophagus is primarily via descending branches of the inferior thyroid arteries and ascending branches of the bronchial arteries, with occasional contributions from the right intercostal artery and the artery of Luschka, a branch of the subclavian artery.[14,15] These arteries course along the posterior and posterolateral surface of the esophagus, with frequent anastomoses across the midline, before penetrating the muscularis externa and forming a submucosal plexus of vessels. The fishbone swallowed by our patient probably punctured a vessel wall after esophageal peristaltic motion and esophageal inflammation, demonstrated by the radiographic lucency around the foreign body, caused gradual erosion of the bone into the artery. This mechanism was described by Sloop and Thomson,[9] who felt that the combination of localized infection and foreign body erosion most frequently caused the aortic perforation resulting in esophagoaortic fistula. Occlusion of the vessel may have occurred initially from the tamponading effect of the blood clot that was present, with the eventual formation of an occluding thrombus preventing further hemorrhage. With no subsequent bleeding episodes or swallowing difficulty after 12 months, there is no evidence to suggest that any other serious injury has occurred in this patient; although the fact is recognized that there are no angiographic data to support or refute the hypothesis of the mechanism and type of vascular injury.

With the information obtained from the previous reports and the present case, a diagnostic and management strategy can be proposed for foreign body perforation of the esophagus with possible vascular injury. First and foremost, any patient with a history of and symptoms consistent with foreign body ingestion presenting with a "signal" aerodigestive hemorrhage should be considered to have esophageal perforation with vascular trauma until it is proved otherwise. Intravenous fluids should be started, and a complete blood count and blood bank sample for type and cross obtained. Diagnostic tests currently available may not always detect esophagoarterial fistulas or aneurysms, but when possible, diagnosis and localization are helpful in planning therapeutic maneuvers. Massive exsanguinating hemorrhage precludes diagnostic studies, and immediate surgical exploration is necessary.

If the patient's condition is stable, the initial diagnostic evaluation should consist of lateral and anteroposterior radiographs of the neck and chest. These may reveal the location of a radiopaque foreign body within the esophagus or surrounding tissues, or demonstrate indirect signs of perforation such as prevertebral widening, soft tissue gas, and pneumomediastinum with both radiopaque and radiolucent objects. For those cases in which the foreign body is not identified on plain radiographs, or the presence of esophageal perforation is not clearly evident, an esophagogram with contrast medium may demonstrate the location of the perforating object and esophageal tear. Experimental and clinical studies support the initial use of an iodinated water-soluble contrast agent such as meglamine diatrizoate.[16,17] If the perforation and foreign body are not demonstrated with water-soluble agents, as may occur in up to 50% of cervical esophageal tears, barium sulfate should be used.[16] Barium has physical properties that allow enhanced visualization of extravasation, and the soft tissue granuloma formation barium causes has few, if any, clinical sequelae.[16,17]

Esophagoscopy is useful in the evaluation whether or not plain radiographs and contrast esophagograms have identified the foreign body and site of injury. Endoscopy has the potential to be not only a diagnostic modality, but in certain select situations a therapeutic procedure as well. In addition to locating and retrieving the perforating object, careful esophagoscopy may demonstrate other findings suggesting the presence of vascular injury. An esophagoarterial fistula or false aneurysm may appear endoscopically as an extrinsic pulsatile mass compressing the esophagus, a punctate ulceration in the mucosa with or without a foreign body, or an active site of hemorrhage.[18] Although studies are not available that confirm the diagnostic value of endoscopy in this setting, the rate of diagnosis with endoscopy in cases of abdominal aortoenteric fistula and aneurysm approaches 50%, supporting its use in esophageal perforation with possible vascular injury.[18,19] Failure to identify any of these lesions does not definitely exclude vascular injury. It should be kept in mind that the risk of exsanguinating hemorrhage occurring with esophageal manipulation or foreign body retrieval during esophagoscopy requires that this procedure be performed in the operating room with preparation to proceed to surgical exploration if necessary.

Endoscopic retrieval of the foreign body along with close observation, intravenous antibiotics, and nothing by mouth may provide successful management in a very select group of patients in whom the risk of further unrecognized major vascular injury is low. On the basis of the outcome of the case presented in this report, those cases with foreign body perforation of the posterior midline cervical esophagus proximal to the aortic indentation, with no clinical evidence of mediastinal or neck infection and no active bleeding after endoscopic removal of the foreign body, may fit into this category. Any continued suspicion of vascular injury, recurrent bleeding, or evidence of infection in this select group of patients certainly necessitates further evaluation with angiography or surgical exploration.

Although the role of angiography in diagnosing vascular injuries resulting from foreign body perforation of the esophagus has not been clearly defined, its use may be beneficial for patients in whom the diagnosis is equivocal but the location of esophageal injury places the aorta or carotid artery and its branches at risk. Cases with evidence of trauma to the thoracic esophagus and lateral walls of the cervical esophagus, as well as those cases in which a perforation exists but no foreign body is found, fit these criteria. To our knowledge, angiography in this setting has been used in only one case, to diagnose a common carotid artery false aneurysm that occurred after ingestion of a fishbone.[11] Results from studies evaluating the diagnostic utility of angiography for blunt and penetrating trauma to the cervical vessels and aortoenteric fistula secondary to aneurysmal or prosthetic erosion may be applicable to vascular injury caused by foreign body perforation of the esophagus. Arteriograms of the cervical vessels have been shown to be very accurate in the assessment of vascular injury following external penetrating or blunt trauma to the neck.[20,21] However, angiography has not proved as useful in the demonstration of abdominal aortoenteric fistula and false aneurysms.[18,22] Even with a limited diagnostic utility in these cases, Shepard and Ernst[18] and Thompson et al[22] feel that aortography should be done in a stable patient, as the finding of extravasation through a fistula or opacification of an aneurysm is definitive evidence of vascular injury useful in guiding surgical repair.

Patients with cervical esophageal injuries in whom no angiographic evidence of vascular injury exists may be able to be treated without surgical exploration, while those with thoracic esophageal perforation and angiographic documentation of the site and extent of vascular damage can undergo a well-planned surgical repair. With a mortality of 100% and an uncertain angiographic diagnostic rate for esophagoaortic fistula, an aortogram that demonstrates no vascular injury should not be used to exclude the diagnosis, and surgical exploration seems warranted.

Indications for surgical exploration and treatment of esophageal perforations are controversial, although reports suggest lower mortality rates with operative drainage and esophageal repair.[12,13] Given the poor prognosis in patients with esophageal perforation and vascular trauma in whom there is failure or delay in recognition of the injury and lack of an aggressive surgical repair, we suggest that surgical exploration in conjunction with a vascular surgeon be performed in any case with equivocal or documented vascular injury following diagnostic evaluation. A complete discussion of the surgical options available for repair of vascular injury is beyond the scope of this report, but general guidelines will be presented. Identification of vascular injury to the common and internal carotid arteries may be approached with direct suture repair, patch grafts, or interposition venous or prosthetic grafts.[21] Isolated injury to the external carotid artery or its main branches can be repaired by ligation of the involved vessel.[21] Trauma to the thoracic aorta may require cardiopulmonary bypass to allow adequate isolation of the injured segment. Resection of the segment containing the fistula or aneurysm, followed by a procedure for prosthetic graft reconstruction or extra-anatomic revascularization such as axillofemoral bypass may be necessary to prevent mortality and provide the best outcome.[18,19] In all cases the esophageal perforation should be identified, judiciously debrided if necessary, and repaired by suture closure and wound drainage. Local tissue flaps interposed over the suture line provide support that will help to prevent esophageal leakage and the formation of a fistula between the sites of esophageal and vascular repair.[12,13]

Thankfully, vascular injury following foreign body perforation of the esophagus is a rare event. Successful management is dependent on prompt recognition of the injury, aided by the history and presence of a "signal" aerodigestive hemorrhage. Efficient diagnostic evaluation with radiographic and endoscopic procedures will help localize the site and extent of injury. In select cases involving the posterior midline cervical esophagus, endoscopic retrieval of the foreign body followed by careful observation and intravenous antibiotics may be adequate therapy. Those patients with persistent hemorrhage, signs of infection, or esophageal trauma directly jeopardizing the aorta or carotid artery and its branches should be aggressively treated with angiography or surgical exploration alone or in combination. Careful repair of the esophageal injury together with repair or ligation of the vascular disruption should help to decrease the morbidity and mortality previously associated with vascular injury following foreign body perforation of the esophagus.

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DIAGNOSIS AND MANAGEMENT OF CLEFT LARYNX

LITERATURE REVIEW AND CASE REPORT

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Laryngeal cleft is a rare congenital laryngeal anomaly that has been recognized more frequently in recent years. It can be a serious problem, consisting of separation of the arytenoids with a fissure resulting from a defect in the fusion of the posterior cricoid cartilage lamina. Dysphagia with aspiration of food is commonly seen with resultant bouts of pneumonia. Surgical repair has been successful in a handful of cases. This communication will review our institution's recent handling of a case successfully treated. The epidemiology, embryology, classification, diagnosis, and suggested treatment regimen for laryngeal cleft will also be outlined.

KEY WORDS — cricoid lamina, laryngeal cleft, tracheoesophageal fistula.

INTRODUCTION

The first description of a common esophagus and trachea was in 1792 by Richter.[1] He performed a digital examination on a choking infant with a common gullet and trachea who later died. No autopsy was performed. Pettersson[2] reported the first successful repair in 1955.

By 1974, only 33 cases were reported in the literature.[3] The number discovered was 129 by 1985.[4] Survivors are a small fraction of those with this diagnosis. Death is common because of multiple anomalies, missed diagnoses, or complications of ventilatory embarrassment. We wish to report an additional survivor and the method of management.

CASE REPORT

A 35-weeks-gestational age boy was born to a 30-year-old gravida 3, para 2 woman at another hospital. She was allegedly a drug and alcohol abuser with no prenatal care. Polyhydramnios was not reported. Meconium-stained amniotic fluid was noted at birth, but none was noted below the vocal cords during laryngoscopy after birth. The infant was admitted directly to that institution's intensive care nursery with mild respiratory distress and stridor. He was treated for sepsis and noted to have intermittent hypoxia. The neonate tolerated feedings poorly, exhibiting choking and regurgitation with hypoxia. At 1 week of age direct laryngoscopy was performed, suggesting "tracheomalacia." A barium swallow study performed by nipple feeding showed contrast filling the tracheobronchial tree (see Figure). A full view of the esophagus was also obtained.

At 10 days of age, the infant was transferred to Thomas Jefferson University Hospital for further evaluation and treatment of possible laryngeal cleft. On admission, examination revealed no dysmorphism. His respiratory rate was 40, with intercostal retractions, stridor, and nasal flaring. Rhonchi were noted bilaterally. The quality of cry was not recorded. Intravenous hyperalimentation and intralipids were instituted for nutrition. The neonate was placed in the prone position to minimize aspiration. There was worsening of the ventilation and hypoxia soon after admission and the neonate was intubated. The next day, a barium study via a nasogastric tube with pullback showed bronchopulmonary spillage consistent with either H-type tracheoesophageal (TE) fistula or laryngeal cleft. Multiple self-extubations, noted in the ensuing hospital days, were later recognized as being due to easy slippage of the endotracheal tube (ETT) into the esophagus. Direct laryngoscopy was performed under general anesthesia at 13 days of age. A laryngeal cleft was diagnosed and the defect was described as a cleft encompassing the cricoid ring and a 2-cm portion of the TE party wall.

Cleft repair was first approached via right lateral pharyngotomy at 17 days of age. By use of a red rubber catheter in the esophagus and an ETT in the trachea, a horseshoe-shaped laryngotracheal defect was identified. The free margin was excised, and the common wall was separated with closure of two separate esophageal and tracheal mucosal layers; 3-0 chromic sutures were used with a Connell-type closure inverting the mucosa in a manner similar to that reported by Cotton and Schreiber.[5] The closure was done up to the level of the upper limit of the cricoid cartilage. The neck was closed with a drain in place. The infant was maintained with only an ETT in place in the prone position. A nasogastric tube was not used to avoid pressure necrosis at the

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Presented at the meeting of the American Broncho-Esophagological Association, Palm Beach, Florida, May 2-3, 1990.

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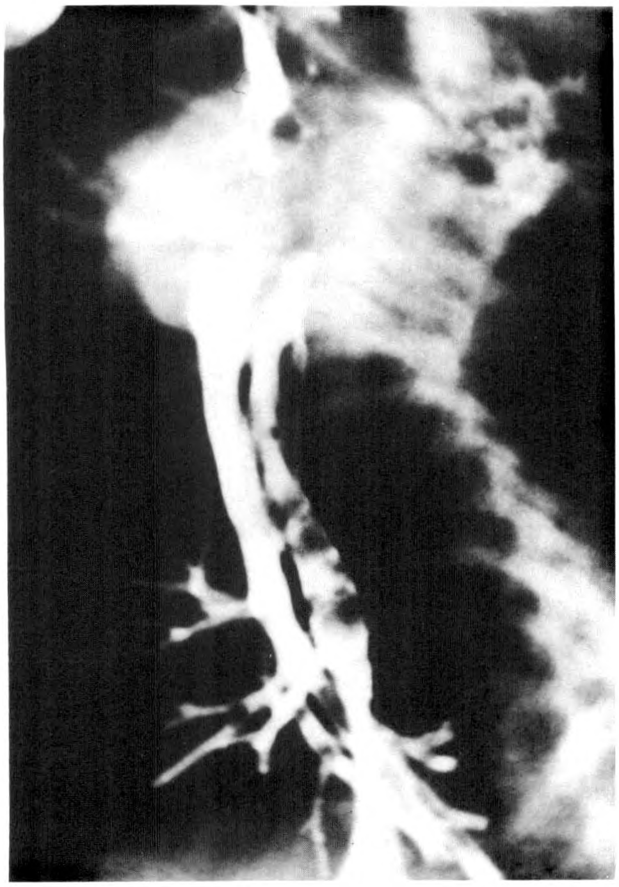

Barium swallow study demonstrates severe aspiration in patient with laryngeal cleft type 2.

closure. Postoperatively, there were multiple self-extubations that were poorly tolerated. Cardiopulmonary resuscitation was briefly administered at 33 days of age.

On postoperative day 7, direct laryngoscopy demonstrated intact closure. Partial breakdown at the level of the cricoid was noted at a subsequent direct laryngoscopy on postoperative day 14. Tracheotomy was then performed, with dramatic improvement in oxygenation and rapid weaning from the ventilator. At 44 days of age, repeat repair of the cleft larynx was performed in conjunction with the insertion of a gastrostomy tube. The second cleft repair of the defect was also approached via right lateral pharyngotomy. The sternocleidomastoid and great vessels were retracted laterally. During the operation it was documented that the cricoid repair had partially broken down. The breakdown was repaired with interrupted 4-0 polyglycolic acid sutures. Similar wound approximation with elevation of two mucosal flaps after freshening the margins was performed. An ETT was used as a stent during repair in both the esophagus and trachea. Postoperatively, the infant did very well, with excellent healing noted during direct laryngoscopy on several occasions.

At 6 weeks of age, significant gastroesophageal reflux was noted, with aspiration. Medical treatment was instituted with bethanechol chloride and, subsequently, metoclopramide hydrochloride. Eventually, fundoplication was performed at 14 weeks of age.

Documentation of a small TE fistula was performed by barium swallow study at 17 weeks of age. Repair was performed by endoscopic cauterization of a small nipplelike protrusion in the trachea with an insulated stylet.

At present, the infant is 15 months of age and being maintained on gastrostomy tube feedings and tracheostomy at a foster home. The child has mild delays in gross motor skills and speech. Repeat barium swallow studies have revealed the cleft to be closed, and decannulation is planned.

DISCUSSION

Embryology and Pathogenesis. The respiratory primordium develops from a diverticulum on the foregut caudal to the pharyngeal pouches at about 25 days. This is termed the tracheobronchial groove or ridge. Subsequently, lateral furrows arise on each side of the diverticulum, which then fuse in the midline in a caudocranial direction to form the TE septum. The separation of the laryngotracheal tube from the esophageal tube is completed by the sixth week of gestation to the level of the first tracheal ring.[6]

The anlage of the cricoid cartilage presents at 5 weeks as a derivative of the inferior portion of the sixth arch.[7] Controversy exists over the initial source of the cartilage formation.

Hast[6] places initial cricoid cartilage chondrification at two lateral centers of cartilage that fuse ventrally at 6 weeks and dorsally at 7 weeks. Zaw-Tun[8] maintains that the cricoid chondrifies from a single ventral center, the lateral margins of which advance dorsally on each side of the infraglottis and meet at about 7 weeks.

Formation of the cleft defect results from interruption of the cephalad development of the TE septum and incomplete fusion of the cricoid lateral rami to form a dorsal lamina. Various arrests in development can result in defects of the interarytenoid region, classified as types 1, 2, and 3, which will be discussed in detail. The fusion of the dorsal cricoid plate and the formation of the TE septum appear to develop independently, and the exact relationship is not clear.[6-10]

The histopathology of the lesion is noted to consist of 1) a cartilaginous defect of the dorsal lamina of the cricoid, 2) partial agenesis of the interarytenoid muscle, 3) lateral subluxation of the cricoarytenoid joint (due to unopposed posterior cricoarytenoid muscles), and 4) normal respiratory epithelium lining the airway.

TABLE 1. SYNDROMES ASSOCIATED WITH LARYNGEAL CLEFT

- Pallister-Hall syndrome (autosomal-dominant)
    - Hypothalamic hamartoblastoma
    - Laryngeal cleft
    - Hypopituitarism
    - Imperforate anus
    - Polydactyly
- G syndrome (sporadic)
    - Dysphagia
    - Hypospadias
    - Hypertelorism
    - Cleft lip and palate

TABLE 2. ANOMALIES ASSOCIATED WITH LARYNGEAL CLEFT

- Tracheoesophageal fistula (12%-20%)
- Laryngomalacia
- Cleft lip and palate
- Subglottic stenosis
- Pulmonary anomalies (tracheal shortening, hypoplastic lungs)
- Cardiovascular defects (transposition of great vessels)
- Hamartomas
- Gastrointestinal abnormalities (imperforate anus, rectal stenosis, mesenteric malrotation, Meckel's diverticulum)
- Genitourinary abnormalities (hypospadias, hypoplastic kidneys)

The loss of vocal ligament abduction and deficient TE septum provides an excellent chance for aspiration. The tendency to airway collapse may be produced by the deficiency of the cartilaginous framework.[7,11]

Classification. The defect in the posterior cricoid lamina may be confined to the larynx above or extend down the TE septum as far caudad as the carina. Classification of such defects as proposed by Evans[12] is based on clinical status. The type 1 or posterior cleft larynx defect is confined to the supraglottic larynx with deficient interarytenoid musculature. The cricoid lamina is intact. The presenting symptom may be coarse inspiratory stridor dating from birth. Diagnosis will depend on careful laryngoscopic examination and possibly microlaryngoscopy with bimanual palpation of the interarytenoid region.

The type 2 cleft defect involves the cricoid lamina and may involve the cervical trachea. Symptoms will vary from poor feeding to coughing and choking due to aspiration from laryngeal incompetence. Recurrent aspiration pneumonia will ensue. This defect is the most common.[9]

The type 3 cleft larynx involves the thoracic trachea as well. Severe cyanosis and aspiration ensue from birth. Certainly the prognosis is poorer with the last group, but reportedly these children can do surprisingly well prior to surgical repair.[12]

Mortality. The mortality rate for cleft larynx defects is quite high. Coexistent major anomalies are commonly present and a search for such problems should be undertaken. Missed diagnoses and underestimation of the severity of the defect certainly contribute to the high mortality.

Overall mortality for all patients with the defect is 46%, including patients with other major anomalies. Approximately 50% of patients in one study underwent surgical cleft repair. Overall postoperative mortality was 25%.[3,9] Mortality is correlated with the extent of the defect.[12]

Morbidity with cleft larynx is related to aspiration pneumonia, impaired nutrition, and frequent association with other congenital defects. The patients are subjected to prolonged tracheostomies. Multiple surgical procedures are required for repair and support. Hospitalization for less than 12 months is unusual.[3]

Epidemiology. Cleft larynx is a rare disorder with an incidence of less than 0.1%. McIntosh[13] reviewed 5,964 pregnancies and found deformities of the respiratory tract in only 0.2% with no case of cleft larynx. Cameron and Williams[14] reported four clefts in a series of 2,000 autopsies at a pediatric hospital. Fearon and Ellis[15] reviewed laryngeal anomalies in 433 cases over a 10-year period and reported two cases of laryngeal cleft. Laryngotracheoesophageal cleft is included in the physical findings in G syndrome and Pallister-Hall syndrome[16] (Table 1).

Familial occurrence has been documented in three families, postulated as autosomal-dominant inheritance. Maternal drug abuse and alcohol abuse are noted in several case reports.[17] Association with other defects is common in the literature.[3,4] Polyhydramnios and prematurity are commonly reported. The most common associated systemic defect is TE fistula. Table 2 outlines the anomalies associated with cleft larynx. It is of clinical importance to note the frequent association of TE fistula in patients with cleft larynx. The incidence may be as high as 20%.[7] Conversely, physicians caring for patients with TE fistula should be aware of the possibility of cleft larynx, especially in those patients with stridor. A common pathogenic mechanism for the lack of separation of the trachea and esophagus may be postulated.

Information on incidence of laryngeal cleft from autopsy studies may be erroneous. It is suggested that the deformity has been previously overlooked by virtue of a postmortem routine in which the larynx is routinely split in the posterior midline.[18] Greater diagnostic yields may be obtained with more awareness of the laryngeal cleft defect.

Clinical Diagnosis. Patients with laryngotracheoesophageal clefts present with aspiration and cyanosis during feeding. Stridor and excess mucous secretions are commonly reported. Various degrees of dysphonia are noted in the literature.[4,5] If the condition is left untreated, repeated bouts of aspiration pneumonia with respiratory compromise and death

TABLE 3. SYMPTOMS OF LARYNGEAL CLEFT

	% of Patients
Aspiration and cyanosis with feeding	53-80
Postpartum asphyxia	33
Excessive secretions	23
Recurrent pneumonia	16
Voiceless crying	16
Stridor	10-50

Adapted from Roth et al[9] and Tyler[4].

are the outcome. Gastroesophageal reflux is a contributing factor to pulmonary embarrassment.[10] The symptoms are relatively proportionate to the severity of the cleft defect.[7] Polyhydramnios and prematurity are present in about one third of the cases reported.[19] Review of the literature outlines the major symptoms and their incidence in laryngeal cleft (Table 3[4,9]).

Evaluation of the newborn with feeding problems, repeated aspiration, and respiratory distress should include analysis for a number of conditions. Most important, examination for choanal atresia and TE fistula as well as the less common laryngeal cleft must be undertaken. It is significant that stridor is not a common finding in TE fistula. Laryngeal cleft can present with a normal voice (small defect), with stridor, or even with aphonia (large defect).[5] Symptoms of laryngeal cleft can be misleading and the diagnosis is often missed.[11]

A complete prenatal and birth history must be taken. Central nervous system lesions from prematurity, congenital infections, maternal drug use, hypoxia, or birth trauma may produce temporary or permanent deglutition deficits. Esophageal disorders such as cricopharyngeal spasm or patulous cricopharyngeal sphincter, cardiospasm, or strictures may produce the picture of aspiration. Contrast studies will differentiate these problems. Neuromuscular deficits such as myasthenia gravis, amyotonia congenita, and autonomic dysfunction of Riley-Day syndrome must be considered as causes for aspiration.[20]

Radiographic studies (Table 4) are commonly performed after complete physical examination. Passing a radiopaque nasogastric tube into the nasopharynx will exclude choanal atresia. Pullback of the catheter from the stomach using contrast during cine-esophagraphy will aid in the evaluation for TE fistula. One should remember that H-type fistula is the rarest form of TE fistula (approximately only 4%). A suggested radiographic approach is that a barium swallow study be done if the voice is normal. If the voice is abnormal, laryngoscopy should be performed with passage of an ETT prior to an esophagram.[21] Laryngeal cleft should be suspected if there is difficulty placing or maintaining the ETT within the tracheal lumen, as in our patient's case. Radiographic diagnosis is often missed because of the relatively obscure nature of the disease. Most often, there is a misdiagnosis of H-type TE fistula rather than cleft. Tracheal soilage is often noted. Radiography cannot always distinguish a high H-type TE fistula from a cleft.

TABLE 4. RADIOGRAPHIC FINDINGS IN LARYNGEAL CLEFT

Hyperaeration
Aspiration pneumonia
Dyskinesis of swallowing
Barium swallow study or catheter pullback procedure demonstrates tracheobronchial soilage of contrast medium

Review of the literature emphasizes the fact that this is often a missed diagnosis. It is not uncommon for several clinicians to examine the patient, with repeated radiographic studies and endoscopies being performed before a diagnosis is made. A high awareness of this potentially life-threatening lesion is necessary.[3,4] Our patient underwent three laryngoscopies and two barium esophageal studies prior to precise diagnosis.

After completion of chest radiography and contrast esophageal swallowing studies, careful endoscopic examination of the upper aerodigestive tract will yield the greatest success rate in definitive diagnosis. Careful endoscopy of the larynx, tracheobronchial tree, and esophagus under general anesthesia is essential. Findings are often subtle and even the experienced endoscopist may miss the diagnosis.[18]

During laryngoscopy and bronchoscopy, redundant tissue is often present in the posterior aspect of the upper respiratory tract. The edges of the cleft tend to approximate with inspiration. An agitated infant undergoing a laryngoscopy may be initially diagnosed as having laryngomalacia or tracheomalacia, as in our case report. Careful endoscopy under general anesthesia is therefore a prerequisite to treatment.[3] An important clinical finding is the herniation of esophageal mucosa into the larynx or trachea, presenting as a soft tissue mass.[22] One should beware of mistaking the normal interarytenoid notch for a cleft malformation.[23] Examination with a nasogastric tube in place may lend itself to cleft diagnosis. Overlying mucosa may also obscure a cartilaginous defect. Lateral subluxation of the cricoarytenoid joint has been noted by some examiners.[20] Use of a magnification telescope will often aid in the diagnosis.[2] Visualization with the ETT in place may often stent the defect, making the cleft obvious.[5] Examination of the cleft larynx may require bimanual palpation with a spatula or right-angle probe.[19,23] Often investigators suggest elevating the larynx with the laryngoscope lip in the vallecula.[11] Advancing an anterior commissure laryngoscope may abduct the cords widely and demonstrate the defect.[18] A laryngeal sound for measuring this defect has been designed.[10] Careful retrograde esophagoscopy may reveal the cleft anomaly. Mathew's forceps or a bronchoscope may be used to

TABLE 5. MEDICAL TREATMENT OF LARYNGEAL CLEFT

Secure airway	Endotracheal tube
	Tracheostomy
	Assisted ventilation
	Antibiotics
Prevent aspiration	Gastrostomy
	Gastric diversion
	Esophagostome
	Fundoplication
Medical evaluation for associated anomalies	Cardiopulmonary
	Gastrointestinal
	Central nervous system
	Genitourinary
Nutrition	Enteral
	Parenteral

palpate the cricoid. In our patient, a careful examination under full paralysis using suction tips as a probe and examination of the postcricoid region using the Jackson sliding laryngoscope to visualize the ETT from the esophagus were utilized during endoscopy to clarify the diagnosis.

Medical Stabilization. Prior to surgical intervention for laryngeal cleft, medical stabilization is necessary (Table 5). Optimal pulmonary and nutritional functioning are of paramount importance. Respiratory compromise is initially managed by endotracheal intubation. Problems with tube maintenance in our patient and other studies[5,7] strongly suggest the need for early tracheostomy. Often the defect is extensive enough to permit the tracheostomy tube to continue to slip into the esophagus, and customizing the tracheal tube may be necessary. After the airway is secured, treatment often necessitates assisted ventilation and antibiotics.

Prevention of aspiration from gastroesophageal reflux is an essential adjunct to cleft treatment. Initial treatment requires positioning in reverse Trendelenburg position. Antireflux medication may be considered for use. Ongoing aspiration is the rule in type 2 and 3 lesions. A nasogastric tube may contribute to ongoing reflux and aspiration or even obstruct the airway. Surgical intervention with gastrostomy and fundoplication, as suggested by Delahunty and Cherry,[11] was utilized in our patient with successful results. Gastric diversion with high total gastric section and lower esophagostomy to prevent aspiration is advocated by Cotton and Schreiber.[5] Gastrostomy alone may be insufficient to control aspiration before and after surgical repair. Reversal of the double gastrostomy is possible, as the neurovascular structures are left intact.[5]

Adequate nutritional support is mandatory for the patient with cleft larynx. If there is a competent gut, enteral feeding is optimal. Parenteral hyperalimentation can be utilized if needed. Associated risks are higher for prolonged parenteral alimentation. Low-flow enteral feedings will minimize regurgitation as compared with bolus feedings.

Medical stabilization and evaluation will optimize the patient's chance to survive the surgical repair.

Surgical Repair. Surgical repair is necessary in most cases of laryngeal cleft. Only patients with type 1 cleft defects have been able to survive without surgery.[12,23] If aspiration of secretions is noted, tracheostomy and gastrostomy with plans for surgical correction are suggested. Type 1 clefts without aspiration might be managed by thickened feeds, gavage, or gastrostomy feedings. Only about one half of patients with type 1 cleft are noted to survive without surgery.[7]

Type 2 cleft larynx is the most commonly diagnosed size of defect, and was seen in our patient. Surgical repair is mandatory for long-term survival. The prognosis rate is worse for patients approached by simultaneous thoracotomy and cervical exploration.[7]

The surgical approach is guided by the exact anatomic defect found and measured during endoscopy. The actual surgical repair is performed in two layers to separate the common esophagotrachea. The repair should proceed as far cephalad as the true vocal cords, but repair of the interarytenoid region is not needed.[5] Some surgeons recommend emcompassing a cuff of esophageal wall to reinforce the tracheal repair.[3] Use of sternocleidomastoid vascularized grafts has been reported.[24]

The anterior approach offers excellent visualization but may render the larynx unstable. Anterior laryngofissure minimizes the possibility of injury to the laryngeal nerves. It requires prolonged stenting and a keel for maintenance of the anterior commissure. It is recommended in the cervical approach to a cleft that extends beyond the third tracheal ring or is greater than 3 cm.[19]

The posterior approach entering the pharynx and esophagus offers a limited view but less danger of laryngeal nerve injury. It is rarely used.[25]

The lateral pharyngotomy is the most commonly used approach. The recurrent nerve is at risk, but is rarely found. True injury is uncommon. It can be used for extensive clefts.[5] The lateral pharyngotomy affords an excellent view of both the laryngeal and esophageal defects for an adequate two-layer closure. Some recommend the lateral pharyngotomy for smaller defects above the third tracheal ring only.[12]

The cervicothoracic approach is advocated for extensive defects or if concurrent thoracic surgery is mandated for correction of TE fistula.[22] Endoscopic repair has been described in older, larger patients with small defects.[9,12] Teflon injection, without cure, has been noted in anecdotal reports.

For fine details and exquisite diagrams the clinician is directed toward those reports emphasizing the techniques of surgical repair.[5,7,12,19,22,24,26]

Complications of surgical repair include laryngeal nerve injury, cleft re-separation, granulation tissue, esophageal stricture, continued aspiration, and late TE fistula.

CONCLUSION

Cleft larynx is an uncommon congenital anomaly involving a defective communication of the midline larynx and trachea with the esophagus. Laryngeal cleft should be included in the differential diagnosis of any neonate with respiratory distress, aspiration, difficulty feeding, and stridor. Case reports are becoming more common and astute awareness is needed to confirm this important diagnosis. If left untreated, repeated bouts of aspiration pneumonia with respiratory compromise and death is the outcome.

Our case report details a near-term neonate with stridor since birth and aspiration pneumonitis with feeding difficulties. The mother was a drug abuser. The neonate underwent two barium esophagograms and three laryngoscopies prior to diagnosis. Two surgical repairs by lateral pharyngotomy were performed. The second was done after breakdown of the first for unknown reasons. The neonate required tracheostomy and gastrostomy.

It is suggested from the literature review and our institution's experience that the infant with laryngeal cleft should undergo early tracheostomy and airway stabilization. Gastric reflux is a significant problem and gastrostomy with an antireflux procedure should be performed as soon as medically feasible. Evaluation for associated anomalies should be undertaken. Major abnormalities of the cardiorespiratory or gastrointestinal tract will alter the infant's surgical eligibility. Examination for TE fistula is especially important.

A multidisciplinary approach is needed for diagnosis, stabilization, and surgical repair. Long-term hospitalization is the rule. Only familarity with the cleft larynx anomaly will enable clinicians to reverse the high morbidity and mortality associated with the disorder.

ACKNOWLEDGMENTS — We thank Mary Catherine Murphy and Louis D. Lowry, MD, for their review of the manuscript.

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Ann Otol Rhinol Laryngol 99:1990

EPIGLOTTIC LARYNGOPLASTY FOR REPAIR OF BLUNT LARYNGOPHARYNGEAL TRAUMA

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Two unique cases of blunt laryngopharyngeal trauma are presented in which identical injuries were sustained to the supraglottic larynx and hypopharynx. Examination of the patients included the use of magnetic resonance imaging to help define the extent of injury. A successful outcome was achieved in each instance by employing the reconstructive technique of epiglottic laryngoplasty to repair the mucosal defects.

KEY WORDS — epiglottic laryngoplasty, laryngopharyngeal trauma, magnetic resonance imaging.

INTRODUCTION

As a result of its protected location below the mandible and above a mobile and compressible trachea, a blunt traumatic injury of the larynx is uncommon. Neck extension and laryngeal exposure at the time of impact will result in a compression against the cervical spine and subsequent cartilaginous and mucosal injury. Although indirect laryngoscopy is a mainstay of diagnosis in laryngeal trauma, multiple injuries and involvement of other systems may preclude laryngeal evaluation. Computed tomography (CT) has been suggested as a reliable means of assessing soft tissue trauma as well as of diagnosing laryngeal fractures.

In this report we describe the evaluation and treatment of two identical cases of blunt laryngopharyngeal trauma. Management of the injuries included control of the airway, CT, magnetic resonance imaging (MRI), and surgical repair using the technique of epiglottic laryngoplasty and mucosal flaps to repair epithelial defects. In cases of blunt laryngopharyngeal trauma, accurate preoperative evaluation of the extent of injury is helpful in considering the technique of epiglottic laryngoplasty as a treatment option.

CASE REPORTS

Case 1. A 38-year-old man was first seen 2 hours after a motorcycle accident in which he hit his neck on a chain stretched across the motorway. He complained of neck pain, odynophagia, dysphagia, and hoarseness, but he had no obvious dyspnea. On examination there was excoriation and ecchymosis of the skin of the neck with palpable subcutaneous emphysema. At indirect laryngoscopy, edema, ecchymosis, and distortion of the upper larynx obscured visualization of the glottic area. Radiographic examinations of the larynx were performed. Neck radiographs failed to reveal a fracture. A CT scan showed anterior separation of the thyroid cartilage with a depressed right thyroid ala as well as marked swelling and hematoma in the preepiglottic space extending into the aryepiglottic folds and arytenoids. The cricoid cartilage appeared normal, as did the cricoarytenoid joints. There was marked soft tissue emphysema of the neck with extension into the mediastinum.

Three days following admission he underwent exploration and repair. Direct laryngoscopy showed avulsion of the thyroepiglottic ligament, edema of the false vocal cords, and laceration with avulsion of the aryepiglottic folds. On surgical exposure of the larynx, two fractures were identified, one at the thyroid angle and one of the right thyroid ala with medial displacement of the anterior fragment. Via an anterior thyrotomy through the anterior fracture site, the epiglottic cartilage was resected submucosally to allow advancement of the mucosa to cover the denuded areas. A Montgomery® stent (Boston Medical Products, Inc; Waltham, Mass) was inserted, cartilage fragments were aligned, and the larynx was closed with wire sutures (Fig 1A). Three weeks later the stent was removed endoscopically and a small granuloma at the anterior commissure was trimmed (Fig 1B). The patient's tracheotomy tube was occluded and sequentially decreased in size and he was extubated. A follow-up direct laryngoscopy 2 months later showed a distorted but unobstructed supraglottic airway, an intact anterior commissure, and good vocal cord mobility. Three years following repair the patient died of an unrelated cause, having had no respiratory difficulty over that time interval.

Case 2. A 23-year-old man was admitted to an outlying hospital in respiratory distress following a traumatic injury to the neck sustained while riding

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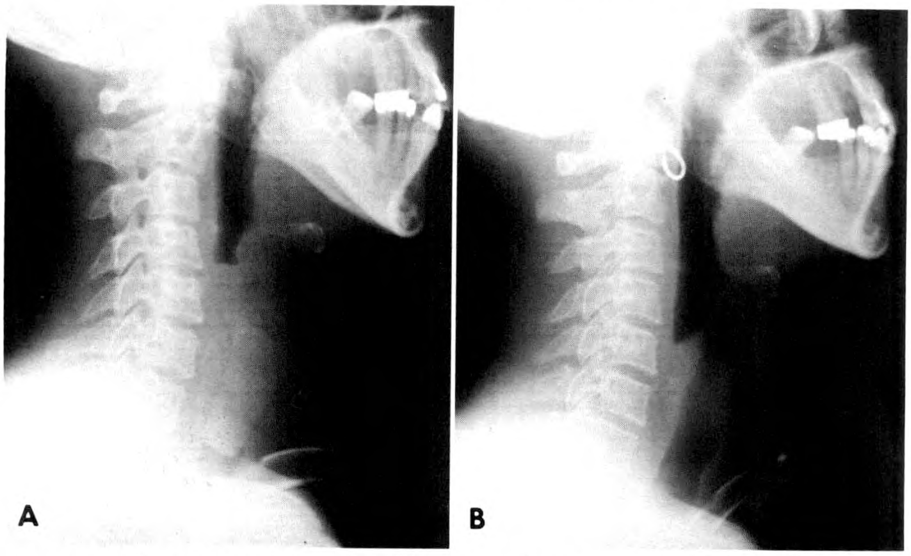

Fig 1. (Case 1) A) Lateral view of neck demonstrating Montgomery® stent in place and absence of epiglottic cartilage. B) Lateral view of neck following stent removal prior to decannulation with patent laryngeal airway.

a motorcycle. Although he was able to vocalize, an emergent tracheotomy was performed to establish an airway, and he was transferred to our institution. On admission, he was noted to have ecchymosis and maceration of the anterior neck skin as well as crepitus in the region of the lower neck and upper chest. The laryngeal landmarks were not well defined, and pain was elicited on palpation of the larynx. Cervical spine radiography (Fig 2) and CT (Figs 3A, 4A, and 5A) were performed. Free air was noted to be present throughout the entire neck, and avulsion of the epiglottis at the base was seen as well. No obvious laryngeal fractures were detected. An MRI scan was then performed in both proton density (T1) and T2-weighted sequences (Figs 3B, 4B, and 5B). Deformity and collapse of the supraglottic larynx above the level of the false vocal cords was seen. Additionally, total opacification of the subglottic space by a collection of blood was seen as inhomogeneous signals in both T1 and T2. No avulsion of the arytenoids was evident.

The patient was taken to the operating room for endoscopy. The vocal cords were noted to be mobile; however, the epiglottis was dislocated from the thyroid cartilage and was elevated to the base of the tongue, thereby eradicating the valleculae. A large right posterolateral pharyngeal laceration with overlying coagulum and bleeding was seen as well.

After a delay of several days the patient returned to the operating room, and the endoscopic findings were unchanged. Neck exploration and anterior thyrotomy were carried out. The larynx was split through a greenstick fracture of the thyroid ala slightly to the left of the midline. Because the thyrohyoid ligament was torn, the hyoid bone was displaced superiorly and a large gap was created between it and the upper end of the thyroid cartilage. The coagulum involving the lacerated aryepiglottic folds was removed to leave a raw surface that was reconstructed by removal of the epiglottic cartilage and preservation of the mucosa to create a laryngeally based flap. A Montgomery® stent was inserted and the larynx was closed with 2-0 Vicryl sutures. Two weeks later the stent was endoscopically removed and a small granuloma at the anterior commissure was trimmed. The tracheotomy tube was occluded, sequentially decreased in size, and finally removed 1 month later.

At that time direct laryngoscopy revealed a distorted supraglottic airway without obstruction, an intact anterior commissure, and good vocal cord mobility. One year later the patient reports no restrictions in his physical activity.

DISCUSSION

Although blunt injuries to the larynx and hypo-

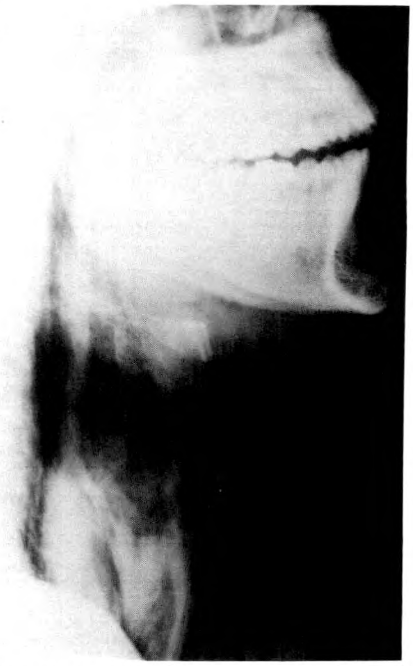

Fig 2. (Case 2) Lateral view of neck with obvious free air dissecting soft tissue planes.

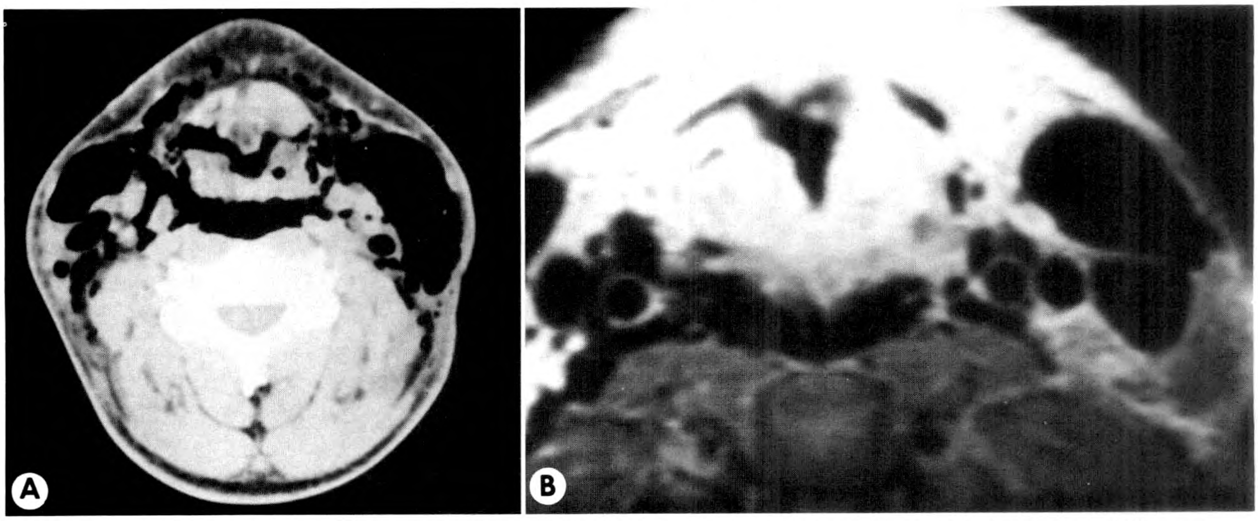

Fig 3. (Case 2) A) Axial computed tomogram of supraglottic larynx revealing gross deformation of epiglottis into ball-like mass. Marked soft tissue emphysema, particularly in prevertebral space, is seen. B) Axial proton density magnetic resonance image demonstrating deformity. Opacification of supraglottic space by collection of secretions and fluid.

pharynx are uncommon when compared to the total number of injuries to the head and neck region,[1,2] failure to recognize and aggressively treat these patients could be catastrophic. Sudden, life-threatening airway obstruction may develop in patients who appear deceptively normal shortly after the insult. Furthermore, incorrect management may result in long-term morbidity with respect to both the airway and the esophagus.

Injury to the laryngopharynx can result from diverse types of trauma. Although motor vehicle accidents and particularly "padded dash syndrome" account for the majority of injuries,[3-5] other causes include hangings,[6] assault,[7] sports injuries,[8] and self-induced trauma.[9,10] Despite the fact that nonpenetrating laryngopharyngeal trauma may present as an isolated injury, it is seen more commonly in the polytraumatized patient.

Correct initial management begins with establishment and control of the airway.[11-14] Although controversy exists as to the best method of obtaining an airway, it is preferable to perform a tracheotomy when confronted with an unstable airway or with a suspected cervical spine injury. After the patient has been stabilized and any associated injuries have been treated, the injury to the laryngopharynx can be evaluated.

Physical examination is considered to be the mainstay of the diagnosis and workup of these patients.[12] Traditionally, indirect laryngoscopy has been advocated as the best method of laryngeal evaluation. Although a surface view of the airway may be obtained, details of deeper injuries to the laryngopharynx may go undetected. Recently, CT has been advocated for confirming the clinical suspicion of fractures as well as for judging the severity

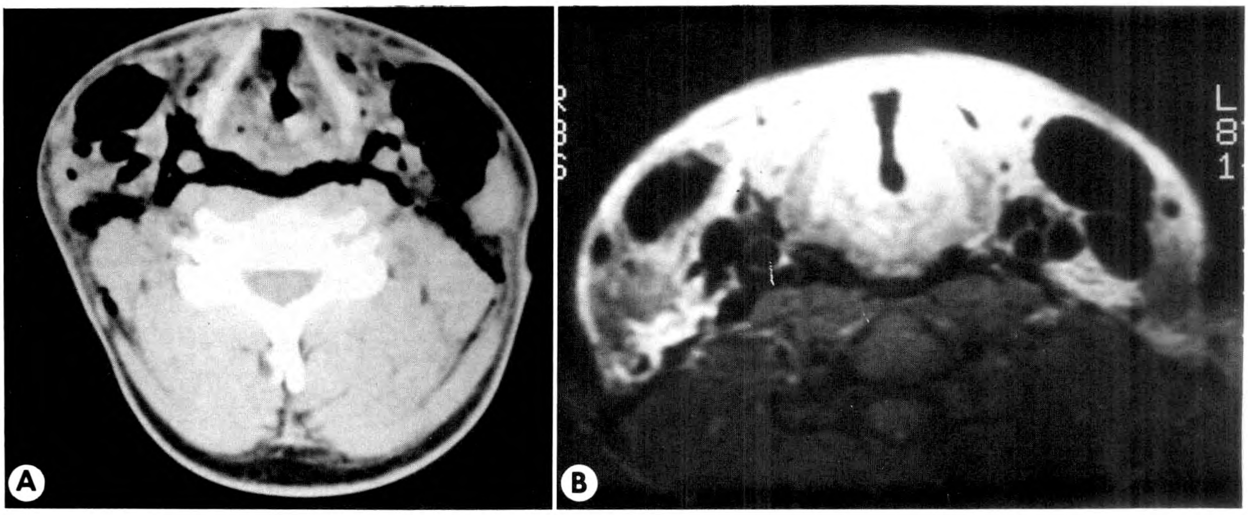

Fig 4. (Case 2) A) Axial computed tomographic view through laryngeal vestibule showing apparent avulsion of false vocal cords from their anterior attachment. B) Axial T2-weighted magnetic resonance image clearly demonstrating submucosal collection of blood at level of false vocal cords. Avulsion at anterior attachment is obvious.

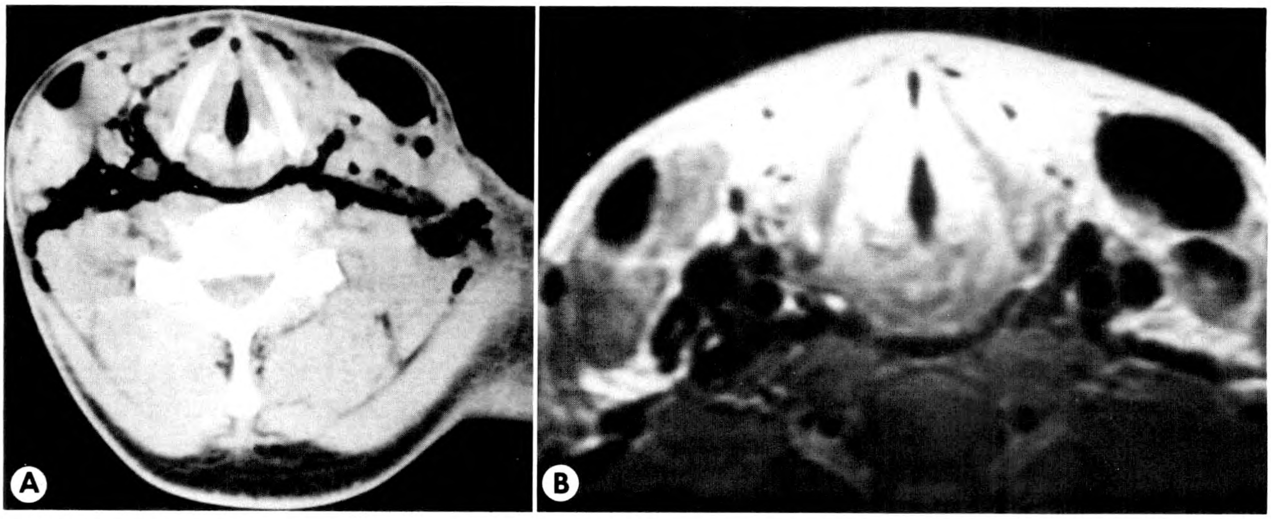

Fig 5. (Case 2) A) Axial computed tomogram at level of glottis showing slight narrowing of airway. There is no evidence of fracture of cartilage. B) Axial T2-weighted magnetic resonance image at level of glottis demonstrating collapse of vocal cords similar to that seen on computed tomogram.

of both soft and hard tissue damage.[15-17] It is an excellent noninvasive technique for examining the laryngeal skeleton. It has been suggested as the diagnostic modality of choice to determine the need for open repair in cases of blunt laryngeal injury.

Since the advent of a specialized neck surface coil used with MRI, improved spatial resolution is available to accurately identify laryngeal architecture.[18] Surface coil MRI has several advantages over CT. Tissues that appear to be of similar density on CT can be easily differentiated on MRI. Muscle, lymphatic tissue, and blood vessels have distinct characteristics that are not discernible on CT. Furthermore, MRI offers multiplanar capability to allow evaluation of thin sections in the axial, coronal, and sagittal planes. Finally, MRI does not require the injection of contrast material or the use of ionizing radiation.

By way of comparison, CT does offer a slight advantage for evaluation of finer details of the cartilaginous architecture, although gross fractures will be evident on MRI. An intact cartilaginous framework may harbor significant soft tissue damage that would be better evaluated with MRI. Edema of the soft tissue deep to the cords may appear as uniform on CT; however, with MRI blood can readily be distinguished from soft tissue swelling. This ability is critical, as it can determine the need and timing for possible operative intervention. Unquestionably, soft tissue damage to the hypopharynx will be more clearly seen on MRI.

In 1976, Olson[19] reported two cases of repair of laryngeal injuries utilizing an epiglottic mucosal flap. An additional two cases were described 9 years later along with a composite cartilage-mucosal flap that was employed in nine other cases.[20] Others have advocated the composite flap to repair defects following laryngeal tumor resection.[21] Regardless of the nature of the injury, the theory of repair emphasizes the need to reline the denuded endolaryngeal mucosa, since healing will be abnormal if raw areas are allowed to heal secondarily. The purpose of lining the endolarynx is to create conditions that will result in primary healing, thereby reducing the development of granulation tissue and scarring. This relining can be accomplished with readily available mucosa from the epiglottis, which itself may not be damaged at the time of injury.

Stenting appears to be a useful adjunct to mucosal repair in cases of blunt laryngeal trauma.[22] By limiting the motion that is inevitable in this area, stenting allows the mucosal lining to heal more naturally without the generation of granulation tissue.

CONCLUSIONS

Epiglottic laryngoplasty can be effectively employed to repair damage to the endolarynx sustained from blunt trauma. In evaluating these injuries prior to repair, MRI is extremely sensitive in determining the nature and extent of damage. Following control of the airway and prior to operative intervention, it should be employed as the diagnostic modality of choice to evaluate injuries to the laryngopharynx.

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Ann Otol Rhinol Laryngol 99:1990

STAGING PROPOSAL FOR EXTERNAL AUDITORY MEATUS CARCINOMA BASED ON PREOPERATIVE CLINICAL EXAMINATION AND COMPUTED TOMOGRAPHY FINDINGS

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An accepted staging system for squamous cell carcinoma of the external auditory meatus is currently lacking and would permit accurate comparison of treatment strategies and results for patients with this unusual neoplasm. In order to develop such a staging system we reviewed the prognostic variables and the accuracy of radiographic diagnoses in 39 patients undergoing temporal bone resection for squamous carcinoma of the external auditory meatus. Predictors of poor survival were extensive tumor involvement, facial nerve paralysis, middle ear involvement, and cervical or periparotid lymphadenopathy. In a comparison of 12 specific anatomic sites, computed tomography was found to be an accurate indicator of histopathologically proven tumor invasion. On the basis of this clinical-radiographic-histopathologic analysis, we propose a TNM staging system for external auditory meatus carcinoma utilizing preoperative computed tomography and physical examination. This system fulfills the requirements of the American Joint Committee on Cancer that a staging system should provide a sound basis for therapeutic planning for cancer patients by describing the survival and resultant treatment of different patient groups in comparable form.

KEY WORDS — external auditory meatus, squamous cell carcinoma, staging, temporal bone cancer.

INTRODUCTION

Carcinoma of the temporal bone is a rare but highly aggressive lesion associated with a poor prognosis. Despite the technical innovation of en bloc resection described in the early 1950s[1] and the surgical advances necessary for cranial base teams to successfully perform true total temporal bone resection,[2] the realistic benefits of these procedures are still unclear.

The absence of an accepted staging system for temporal bone carcinoma seriously impedes rational comparison of clinical series and their reported treatment efficacy. A reliable staging system requires criteria to separate patients into groups with different prognoses and a method to reliably determine these criteria before treatment begins.

Clinical reports of patients with temporal bone cancer have used different systems for dividing patients into prognostically significant groups based on the pathology review of temporal bone resection specimens. These lesions have been categorized according to site of anatomic origin, pathologic differentiation, and local invasiveness. The prognosis of squamous cell carcinoma of the external auditory meatus (EAM) is mostly related to the extent of the primary lesion. The authors' institution recently presented a preliminary report of 35 patients with squamous cell carcinoma of the EAM in which patients were divided into three categories: 1) category A, in which the lesion was limited to the EAM without erosion, 2) category B, with tumor eroding the osseous EAM or involving the middle ear and/or mastoid, and 3) category C, with involvement of the cochlea, dura, medial wall of the middle ear, petrous apex, or surrounding soft tissue. Reduced survival was noted with more advanced and extensive lesions.[3]

Preoperative staging in temporal bone cancer is particularly difficult, since much of the organ is inaccessible to direct examination. Kinney[4] has reported that the medial EAM and tympanic membrane were only visible in 50% of his series of 30 patients. Historically, radiographic assessment of temporal bone lesions based on plain films and tomograms was unreliable. However, high-resolution computed tomography (CT) represents a significant improvement in assessing temporal bone malignancies.[5] We have recently determined that preoperative CT is extremely accurate in delineating the extent of squamous cell carcinoma of the EAM.[6]

As a basis for a TNM staging system, this study is a radiographic-clinical-histopathologic correlation analysis of our experience with EAM squamous cell carcinoma.

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TABLE 1. SUMMARY OF CLINICAL AND PATHOLOGIC CHARACTERISTICS IN 39 PATIENTS WITH SQUAMOUS CELL CARCINOMA OF EXTERNAL AUDITORY MEATUS

Patient	*Pathologic Extent*	*Surgery*	*Margin Status*	*Nodes*	*Survival*	*T Stage*	*TNM Stage*
1	B	PTB	–	–	NED (97 mo)	T3	III
2	C	TTB/ND	–	–	DOD (9 mo)	T4	IV
3	B	PTB	–	–	NED (96 mo)	T3	III
4	C	TTB/ND	–	–	DOD (18 mo)	T4	III
5	B	STB	–	–	NED (84 mo)	T3	III
6	B	PTB	–	1 Par	DOD (10 mo)	T3	IV
7	B	STB	+	–	NED (96 mo)	T3	III
8	B	PTB/ND	+	–	NED (42 mo)	T3	III
9	B	PTB	+	–	DOD (6 mo)	T3	III
10	B	PTB/ND	+	–	DOD (23 mo)	T3	III
11	C	STB	+	–	DOD (6 mo)	T4	IV
12	C	PTB	+	–	DOD (11 mo)	T4	IV
13	B	RM/Sleeve	+	–	IFU (7 mo)[a]	T3	III
14	B	PTB	–	–	NED (72 mo)	T3	III
15	B	STB	+	1 Par	DOD (12 mo)	T4	IV
16	C	STB	+	–	NED (132 mo)	T4	III
17	B	PTB	+	–	DOD (7 mo)	T3	III
18	B	RM	–	–	DOD (6 mo)	T3	III
19	B	PTB	–	–	NED (48 mo)	T3	III
20	B	PTB/ND	–	–	DOD (96 mo)[b]	T3	III
21	A	PTB/ND	–	–	NED (62 mo)	T3	III
22	B	PTB	–	–	NED (94 mo)	T2	II
23	B	PTB	+	2 Cer	DOD (11 mo)	T3	IV
24	B	PTB/ND	+	1 Cer	NED (73 mo)	T3	IV
25	A	PTB	–	–	NED (36 mo)[c]	T1	I
26	A	PTB	–	–	NED (82 mo)	T1	I
27	C	TTB	+	1 Par	DOD (11 mo)	T4	IV
28	C	TTB	–	1 Par	NED (27 mo)	T4	IV
29	C	TTB	+	–	DOD (9 mo)	T4	IV
30	A	PTB	–	–	NED (28 mo)	T1	I
31	B	STB	–	–	NED (31 mo)	T3[d]	III
32	B	PTB	+	–	IFU (8 mo)[e]	T3	III
33	B	PTB	+	–	DOD (13 mo)	T4	IV
34	C	TTB	–	–	DOD (Periop)[f]	T4	IV
35	B	PTB	–	–	DOD (Periop)[g]	T3	III
36	A	PTB	–	–	IFU (13 mo)[h]	T1	I
37	C	PTB	+	–	IFU (13 mo)[h]	T4	IV
38	C	TTB	+	1 Cer	DOD (12 mo)	T4	IV
39	C	TTB	+	–	DOD (23 mo)	T4	IV

A — involving external meatus without erosion, B — bone erosion or involvement of middle ear and/or mastoid, C — involving cochlea, dura, petrous apex, or surrounding soft tissue, PTB — partial temporal bone resection, STB — subtotal temporal bone resection, TTB — total temporal bone resection, RM — radical mastoidectomy, Sleeve — sleeve resection, Par — parotid nodes, Cer — cervical nodes, ND — sleeve resection, NED — no evidence of disease, IFU — insufficient follow-up, DOD — dead of disease, Periop — perioperative.

[a] Died of unrelated causes at 7 mo.

[b] Cervical metastases at 36 mo.

[c] Died of unrelated causes at 36 mo.

[d] Anterior extension through cartilage without erosion.

[e] Died of unrelated causes at 8 mo.

[f] Perioperative cerebral ischemia.

[g] Perioperative myocardial infarction.

[h] No evidence of disease.

METHODS

Clinical Series. The hospital charts of 39 patients treated in our institution for squamous cell carcinoma of the EAM from 1974 to 1989 were retrospectively reviewed. Updated follow-up information was obtained from the private office records of the treating physician, the tumor registry, and phone calls to patients or their families.

Patients were considered to have no evidence of disease (NED) after a minimum of 2 years of disease-free follow-up. Pathologic margins were involved (positive) if tumor extended within one high-power field of the limit of resection.

Radiography-Pathology Correlations. A radiography-pathology correlation analysis was performed by selecting those 13 patients in our series who received high-resolution preoperative CT scans of the temporal bone. The CT scans were systemati-

TABLE 2. SURVIVAL IN 39 PATIENTS WITH SQUAMOUS CARCINOMA OF EXTERNAL AUDITORY MEATUS ACCORDING TO EXTENT OF DISEASE AND SURGICAL MARGINS

Pathologic Extent of Disease	*N*	*Free Margins*			*Involved Margins*		
		NED	*DOD*	*IFU*	*NED*	*DOD*	*IFU*
A	5	4	0	1	0	0	0
B	22	7	4	0	3	6	2
C	12	1	3	0	1	6	1
Total	39	12	7	1	4	12	3

A — external meatus without erosion, B — bone erosion or involvement of middle ear and/or mastoid, C — involving cochlea, dura, petrous apex, or surrounding soft tissue, NED — no evidence of disease, DOD — dead of disease, IFU — insufficient follow-up.

TABLE 3. SURVIVAL IN 39 PATIENTS WITH SQUAMOUS CARCINOMA OF EXTERNAL AUDITORY MEATUS ACCORDING TO SURGICAL PROCEDURE AND SURGICAL MARGINS

Procedure	*N*	*Free Margins*			*Involved Margins*		
		NED	*DOD*	*IFU*	*NED*	*DOD*	*IFU*
PTB	23	9	3	1	2	6	2
STB	6	2	0	0	2	2	0
TTB	8	1	3	0	0	4	0
RM	2	0	1	0	0	0	1

PTB — partial temporal bone resection, STB — subtotal temporal bone resection, TTB — total temporal bone resection, RM — radical mastoidectomy, NED — no evidence of disease, DOD — dead of disease, IFU — insufficient follow-up.

cally reviewed for tumor involvement in 12 anatomic areas: external osseous meatus erosion anteriorly, posteriorly, inferiorly, and superiorly; infratemporal extension; middle ear involvement; otic capsule erosion; mastoid involvement; jugular fossa erosion; carotid canal erosion; tegmen erosion with middle fossa involvement; and posterior fossa involvement. A radiologist (H.C.) reviewed the CT scans without knowledge of the histopathology findings or clinical outcome in these cases.

The histopathology slides for the corresponding patients were reviewed according to the same criteria as the CT scans. The pattern and extent of spread were recorded for each case reviewed.

Proposed Modification in Histopathology Technique. During the review it was noted that many anatomic areas of the surgical resection specimen that were described in the operative note and pathology description of the gross specimen were not included in the histopathology sections. Specific note was made of those anatomic areas on which histopathology analysis was not performed. In order to demonstrate that whole organ sectioning of EAM lesions was possible while maintaining anatomic orientation, a partial temporal bone resection was performed on a cadaver specimen from the human temporal bone anatomy laboratory of the Department of Otolaryngology, University of Pittsburgh. The specimen obtained from this formalin-fixed half-head was decalcified in Cal-Ex (Fisher Scientific). After being dehydrated through a series of increasing concentrations of ethanol and cleared in xylene, the tissue was infiltrated with Ameraffin tissue embedding medium (Baxter Scientific Products) under vacuum and embedded in the same material after 3 hours. Sections were made on a rotatory microtome at 14 μm. The tissue was most easily cut when the block was cooled to 4°C to 10°C prior to cutting. The sections were stained with hematoxylin (Harris Modified, Fisher Scientific) and eosin Y (Sigma).

Staging System. A TNM staging system was formulated on the basis of the results of the clinical series, the pathology findings from temporal bone resections, and the accuracy of CT scans in predicting histopathology results (see Discussion). In order to assess the validity of the staging system, the clinical series was staged according to the proposed system.

RESULTS

Clinical Histopathology Series. Thirty-nine patients were treated for squamous cell carcinoma of the EAM from 1974 to 1989 in the Department of Otolaryngology of the Eye and Ear Hospital at the University of Pittsburgh. The series included 23 women and 16 men with a range in age from 59 to 92 and a mean age of 69 years. The details of the clinical presentation, previous therapy, and the operative procedures performed are described in detail in our initial report of this series.[3] Table 1 outlines the survival of each patient according to pathologic extent of lesion, procedures performed, status of surgical margins, and lymph nodes. The 2-year determinate survival rate for this series was 46%. Table 2 summarizes this series according to extent of lesion and the status of pathologic margins. In those patients with adequate follow-up, category A had 100% survival, category B had 50% survival, and category C had 18% survival. When all categories were combined, patients with clear pathologic margins had a 63% survival, whereas patients with pathologically involved surgical margins had a 25% survival. Pathologically involved lymph nodes were an ominous sign. Patients with involved lymph nodes had only a 29% survival. All patients who were dead of disease died from local recurrence. The average interval from local recurrence to death was 3.6 months. As emphasized in our original report,[3] decreased survival occurred with histopathologically positive margins, despite the extent of the surgical resection. Patients who underwent partial temporal bone resections with negative margins had a 75% survival, whereas those with involved margins had a 25% survival. Positive margins following subtotal temporal bone resection were associated with a 50% survival, whereas all patients who required total temporal bone resection and had positive margins were dead of disease. Unlike our original report,[3] however, we now have one patient who is free of disease 2 years following a total temporal bone resection with free pathologic margins (Table 3). The perioperative mortality of this series was 5%, which is consistent with that reported in the literature.

TABLE 4. FINDINGS ON PATHOLOGY AND PREOPERATIVE COMPUTED TOMOGRAPHY OF INVOLVEMENT OF EXTERNAL AUDITORY MEATUS SQUAMOUS CELL CARCINOMA ACCORDING TO ANATOMIC REGION (PATHOLOGIC/RADIOGRAPHIC)

	Patient Number												
Anatomic Region	*1*	*2*	*12*	*15*	*19*	*21*	*27*	*28*	*29*	*30*	*31*	*32*	*33*
Anterior canal	+/+	+/+	+/+	+/+	+/+	+/+	+/+	+/+	+/+	+/+[a]	+/−[b]	+/+	+/+[c]
Superior canal	+/+	+/+	+/+	+/+	+/+	0/−	+/+	+/+	+/+	−/−	+/+	+/+	+/+
Posterior canal	−/−	+/+	+/+	+/+	+/+	+/+	+/+	+/+	+/+	−/−	+/+	+/+	+/+
Inferior canal	−/−	+/+	+/+	+/+	+/+	−/−	+/+	+/+	+/+	−/−	+/+	+/+	+/+
Infratemporal extension	−/−	+/+	+/+	0/0	−/−	0/+	+/+	−/−	+/+	−/−	+/+	−/−	+/+
Middle ear	0/+	+/+	+/+	+/+	+/0	0/−	+/+	0/−	+/+	−/−	0/0	0/−	+/+
Otic capsule	0/−	0/+	+/+	0/+	0/0	0/−	0/+	0/−	+/+	−/−	0/0	0/−	−/+[d]
Mastoid	0/+	+/+	0/+	+/+	0/0	0/−	+/+	0/+	+/+	−/−	+/+	0/+	+/+
Jugular fossa	0/−	−/−	−/−	0/+	0/0	0/−	+/+	0/−	0/+	0/0	0/0	0/−	0/−
Carotid canal	0/−	−/−	−/−	0/−	0/0	0/−	+/+	0/−	0/+	0/−	0/0	0/−	0/−
Tegmen and/or middle fossa	0/−	−/0	0/−	0/−	0/0	0/−	0/−	0/−	+/+	0/0	0/0	0/−	0/−
Posterior fossa	0/−	+/+	0/+	0/+	0/0	0/−	+/+	0/−	−/−	0/0	0/0	0/−	0/−

Plus indicates involvement, minus indicates no involvement, zero indicates that data not available.

[a] Soft tissue only.

[b] False negative (anterior extension without erosion).

[c] Anterior extension to glenoid fossa on pathology and computed tomography.

[d] False positive (promontory mucosa negative for tumor with computed tomographic suggestion of tumor).

Radiography-Pathology Correlation. We have previously described the high accuracy of preoperative CT scan in predicting the pathology findings of squamous cell carcinoma of the EAM.[6] In 96 discrete comparisons in which radiography and pathology data were available, CT scan was accurate in 94. There was one false negative in which the CT scan did not diagnose soft tissue extension without bony erosion through the anterior canal wall. The one false positive occurred in the middle ear on the promontory where the CT scan predicted involvement of the otic capsule. Mucosal biopsy of this area proved to be negative for tumor involvement.

Table 4 contains the detailed results of tumor involvement according to the histopathology of surgical resection specimens and the preoperative CT scans in the 13 patients with both data available. This study identified one previously undescribed pattern of local extension for EAM squamous cell carcinoma. Concentric erosion of the osseous EAM was present in 70%. Extension of disease medial to the tympanic membrane was an ominous finding. Among this subgroup, extension to the middle ear was associated with an 86% disease-related mortality. Involvement of the otic capsule was identified in two patients, and both died of their disease. Infratemporal extension was identified in six patients and associated with an 83% disease-related mortality.

Extensively destructive lesions are easily diagnosed (Fig 1); however, systematic review of the preoperative CT scans is necessary to identify subtle signs of soft tissue extension such as obliteration of fat planes (Fig 2). The CT scans were accurate in identifying even mild degrees of bone erosion (Fig 3).

General Pathology Findings. The pathology examination of temporal bone resection specimens is not standardized. Consequently, the orientation of the specimen, the distance between histopathology sections, and the total number of histopathology sections from a specimen depend entirely on the diligence of the pathologist to whom the case was assigned. Substantial portions of these surgical specimens were discarded without histologic processing or microscopic examination. Although portions of the otic capsule were included in 6 of the 13 resected specimens reviewed, only one histopathology section of one case included the inner ear. Technically, the most difficult part of the pathology review in this study was appropriate orientation of the EAM sections. Despite submission of this portion of the resection as an en bloc specimen in all 13 cases, histopathology sections were not made sequentially through the EAM. Figure 4 is a representative histopathologic section perpendicular to the long axis of the EAM from a normal, preserved, ca-

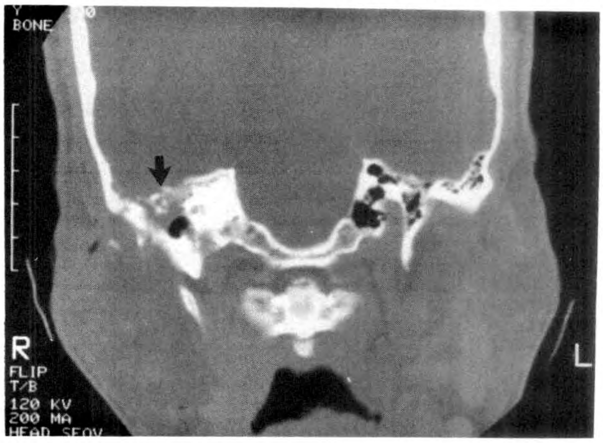

Fig 1. Coronal computed tomogram of advanced carcinoma of external auditory meatus. Erosion of otic capsule, tegmen, middle ear, and mastoid was present. Arrow — tegmen erosion.

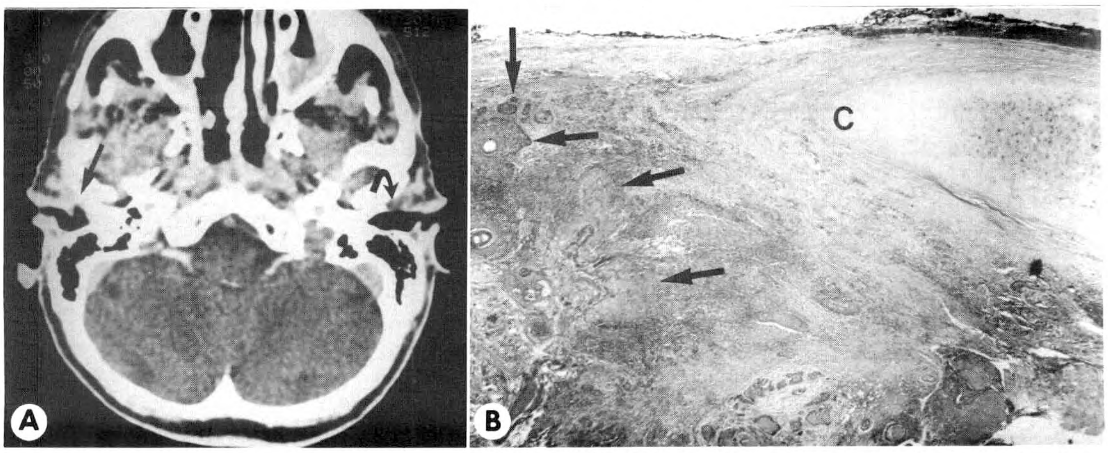

Fig 2. A) Computed tomogram illustrating subtle findings of anterior soft tissue extension of tumor. Fat plane (curved arrow) that is anteroinferior to external auditory meatus on uninvolved side is obliterated on involved side (straight arrow). B) Histopathology specimen from same patient. Note tumor extension adjacent to intact cartilage and inked surgical resection margin. C — cartilage, arrows — tumor.

daver half-head subjected to the usual decalcification and staining techniques used in standard histopathology preparation of surgical specimens. However, the sections were mounted on oversized, otopathology research microscope slides. This combination of routine histopathology techniques with the mounting methodology of otopathology research preserved the anatomic orientation of the specimen.

DISCUSSION

Comparing clinical series of patients with temporal bone carcinoma is confusing. Although primary squamous cell carcinoma of the EAM is the most frequent malignancy of the temporal bone, reported series often include an assortment of primary lesions, metastatic lesions, and tumors with secondary extension to the EAM. This study was limited to EAM squamous cell carcinoma in order to eliminate the possible confounding variable of including a scattered assortment of other histologic lesions.

In this series of primary squamous cell carcinomas of the EAM, we have confirmed that the local extent of the primary lesion is the main prognostic factor. This series has further emphasized the crucial role of clear margins in the surgical resection of temporal bone cancer. This series demonstrated a 79% survival rate when clear margins were present with a partial or subtotal temporal bone resection.

The critical issue is to accurately determine the extent of tumor involvement preoperatively. In this series preoperative CT scans achieved 98% accuracy in predicting pathologic involvement in the temporal bone resection specimens. The radiologist was blinded to the results of the histopathology findings in these cases. However, by systematic assessment of 12 discrete anatomic areas, the findings on preoperative CT scans accurately assigned all patients to the correct categories of pathologic tumor extension that were subsequently verified on the respective patient's histopathology slides. This is not to suggest that CT scans are without limitations in assessing temporal bone cancers. Distinguishing mucosal inflammation from tumor and identifying tumor extension without bony erosion are both difficult with CT. The false-negative finding in this comparison was the result of anterior soft tissue extension without EAM erosion. Imaging technology is continuing to improve. Although magnetic resonance imaging is not as helpful as CT in the assessment of bony involvement by tumor, it has been particularly helpful in assessing soft tissue extension by tumor in other head and neck sites, such as the hypopharynx.[7] Accordingly, it may be helpful in identifying soft tissue involvement around the temporal bone. Thus, we would suggest continued use of this modality as an adjunct to CT scans, since this specialized technology may be able to provide additional information suggestive of tumor involvement.

We disagree with the claim that preoperative staging of temporal bone carcinoma is inherently inaccurate.[4] Some authors have even suggested that this difficulty in preoperative staging justifies abandoning attempts at en bloc resection of tumor in favor of piecemeal resection of gross tumor and postoperative irradiation.[4,8] A basic principle of surgical oncology is complete tumor extirpation. Postoperative irradiation does not substitute for clear (negative) margins in squamous cell carcinoma of the head and neck.[9] Before adopting such a drastic change in treatment philosophy for temporal bone carcinoma, we feel that it is important that current methods be thoroughly tested. Such comparisons are only possible with a staging system.

The American Joint Committee on Cancer[10] states that the goal of a staging system is to evaluate the efficacy of treatment and to provide a sound basis for therapeutic planning in cancer patients by describing in comparable form the survival and results of treatment of different patient groups. The cate-

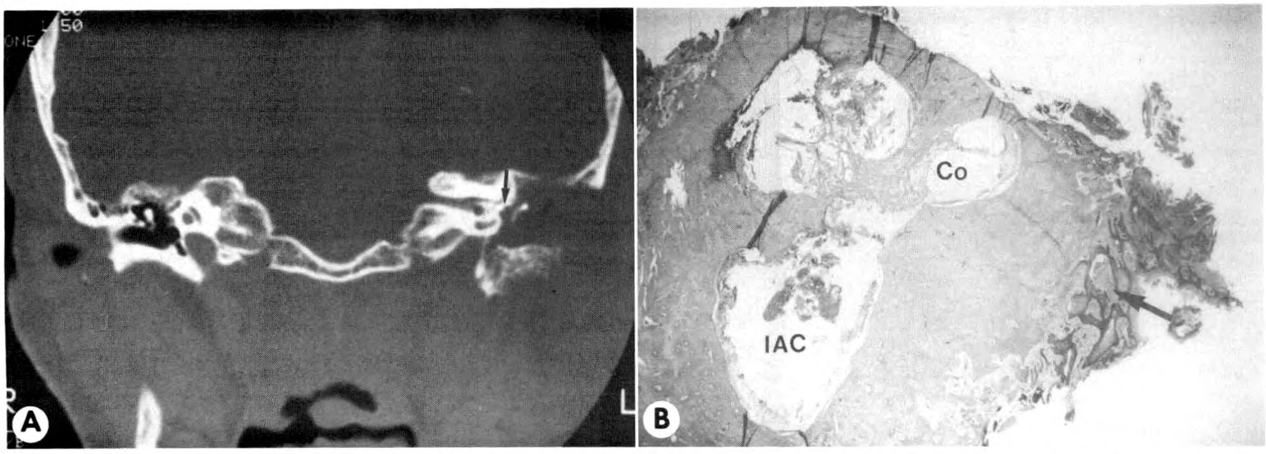

Fig 3. A) Coronal computed tomogram demonstrating erosion of promontory (arrow). B) Histopathology specimen from same patient. Note erosion of basal turn of cochlea (Co) without actual penetration by tumor (arrow). IAC — internal auditory canal.

gories of pathologic extension described in this series demonstrated prognostic value; furthermore, they were reliably predicted with preoperative CT scans. We propose a staging system for EAM squamous cell carcinoma based on preoperative CT findings and supplemented with clinical findings.

T Status. Tumor limited to the EAM without bony erosion or evidence of soft tissue extension would be considered T1. Tumor with limited EAM bone erosion (not full thickness), or radiographic findings consistent with limited (less than 0.5 cm) soft tissue involvement would be T2. This category includes lesions that extend through preformed pathways such as the cartilaginous fissures or bone-cartilage junction of the EAM. Tumor eroding the osseous EAM (full thickness) with limited (less than 0.5 cm) soft tissue involvement, or tumor involving the middle ear and/or mastoid, or patients presenting with facial paralysis would be considered T3. Tumor eroding the cochlea, petrous apex, medial wall of the middle ear, carotid canal, jugular foramen or dura, or with extensive soft tissue involvement (greater than 0.5 cm) would be T4.

N Status. Involvement of lymph nodes is a poor prognostic finding in these patients. For purposes of accurate description, the current American Joint Committee system for classifying lymph node involvement with head and neck neoplasms should be applied. However, any node involvement should automatically be considered advanced disease, ie, T1, N1 = stage III; T2, T3, T4, N1 = stage IV.

M Status. Although no distant metastases were identified in this series, their presence would certainly indicate a poor prognosis. M1 should therefore be considered stage IV disease. In the absence of metastatic lymph nodes or distant metastases, T status of the tumor defines the overall clinical stage of the patient.

Table 5 lists the staging of the entire series. In order to assess the validity of this staging system, T status is listed according to survival status. Complete retrospective preoperative staging data were available in 13 of the 39 patients. By showing that preoperative CT scans accurately predicted histopathologic findings, we were justified in staging the remaining patients with pathologic findings alone (for the purpose of assessing the accuracy of the staging system in predicting survival). This staging system for squamous carcinoma of the EAM predicted the survival of the patients in our series.

Existing classifications for temporal bone carcinoma are either based primarily upon the clinical examination or else include all cancers of the ear. Goodwin and Jesse[11] include cancers of the concha in their stage I classification, and combine all EAM lesions into stage II (including cancers of the external canal and adjacent tympanic membrane without actual middle ear involvement). In 1985, Stell and McCormick[12] proposed a T-staging system based on 33 tumors of the external canal and 14 of the middle ear. However, 10 of their EAM lesions

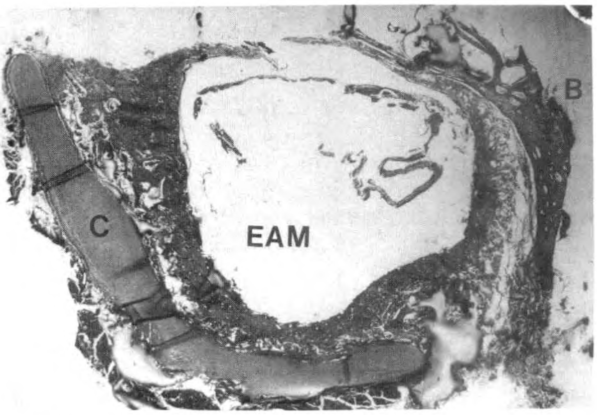

Fig 4. Low-power photomicrograph of partial temporal bone resection from preserved cadaver from temporal bone dissection laboratory. Section is perpendicular to long axis of external auditory meatus (EAM) at bone-cartilage junction. Postmortem changes are present; however, note that anatomic orientation and basic cellular morphology are maintained. C — cartilage, B — bone.

TABLE 5. TUMOR STATUS OF 39 SQUAMOUS CELL CARCINOMAS OF EXTERNAL AUDITORY MEATUS

T Stage	*N*	*NED*	*DOD*	*IFU*
T1	5	4	0	1
T2	1	1	0	0
T3	20	10	8	2
T4	13	2	10	1

NED — no evidence of disease, DOD — dead of disease, IFU — insufficient follow-up.

were of histopathologic cell type other than squamous cell carcinoma, and 10 of their EAM carcinomas were categorized as nonstageable because of insufficient information. A very unusual feature of their series of patients is that 70% of the tumors they staged were T1 lesions (tumor limited to the site of origin, ie, with no facial nerve paralysis and no bone destruction on radiography). The American experience with EAM carcinoma has not been comparable to this British experience of identifying EAM tumors at such an early stage. In contrast, EAM carcinoma in the United States is characterized as an insidious process in which diagnosis is delayed because of its shared symptoms with chronic infection. The Stell and McCormick staging system is difficult to evaluate. Patients were assessed with a generalized statistical model in which overall physical status was a more significant variable for patient survival than tumor stage. Analysis by determinate survival data would more accurately correlate extent of disease with survival.

In addition to clinical findings, our staging system is based on preoperative CT scans, which this radiography-pathology study has validated as a reliable predictor of histopathology findings. Our system provides an objective basis for comparing the survival among series of EAM squamous cell carcinoma patients, and it provides a consistent framework to evaluate the efficacy of treatment modalities. The latter is particularly important with the developing conflict in the literature between those who advocate more radical en bloc temporal bone resections and those who advocate piecemeal resection of gross tumor. Arena and Keen[13] observed that no series of temporal bone carcinoma has shown better survival "than that found with en bloc temporal bone resection and radiotherapy." We have outlined our management strategy and reported in detail the clinical characteristics of our series. We continue to endorse en bloc temporal bone resection followed by postoperative radiotherapy. In addition, we urge that reports of temporal bone carcinomas include detailed clinical information and survival data according to a TNM staging system. Temporal bone carcinoma is unusual, and our patients must benefit from the shared experience of many clinicians who have treated patients with these lesions.

Finally, the pathology examination of temporal bone resection specimens is an important source of information to understand the biology of these unusual lesions. Since these tumors are rare, general pathology departments may not fully examine these specimens because of their unusual orientation and technical problems. In this series, it was quite difficult to ascertain the pathologic status of potential routes of tumor extension because of the manner in which these specimens were prepared. Furthermore, important information concerning the behavior of this lesion in the inner ear was lost when portions of the resected specimens were not examined with histopathologic techniques.

One solution to this problem illustrated in this study was combining techniques of research otopathology with standard histopathology techniques. Another technique that could speed processing time and maintain the anatomic orientation of the specimen is to systematically cut these surgical specimens into several blocks before decalcification. If the specimens were sectioned parallel to the long axis of the EAM, the blocks could be sliced serially and perpendicular to the long axis. Thus, every histology section would show a cross section of EAM. Whatever method is chosen, the surgeon must communicate with the pathologist to assure accurate examination of the resection specimen.

CONCLUSIONS

1. Squamous cell carcinoma of the EAM is an aggressive lesion in which the best results will be obtained by treating these patients with temporal bone resection (in which the margins of resection are free of tumor) and postoperative radiotherapy.

2. Preoperative CT scans can accurately stage patients with squamous cell carcinoma of the EAM.

3. Our proposed staging system facilitates the exchange of clinical data in a comparable form; patient information can be shared to develop the optimal treatment for this rare tumor.

4. Close cooperation with the pathologist examining the temporal bone resection specimen is essential. In this way the biology of this unusual tumor can be studied more fully, and potentially important data will not be discarded because of technical problems in processing the resection specimen.

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FIFTH INTERNATIONAL SYMPOSIUM RECENT ADVANCES IN OTITIS MEDIA

The Fifth International Symposium on Recent Advances in Otitis Media will be held May 20-23, 1991, at the Sheraton Bal Harbour in Bal Harbour, Florida. For further information, contact David J. Lim, MD, 4331 University Hospitals Clinic, 456 W Tenth Avenue, Columbus, OH 43210; Phone: (614) 293-8103; Fax: (614) 293-5506.

Ann Otol Rhinol Laryngol 99:1990

VENTILATION TUBE DURATION VERSUS DESIGN

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Two ventilation tube designs were simultaneously compared in children in order to determine their relative rates of extrusion. The results show a twofold difference between the extrusion of the Shepard compared to the "Sheehy" or collar-button pattern of tube. Subjected to statistical analysis, these findings are highly significant.

KEY WORDS — chronic secretory otitis media treatment, middle ear effusion treatment, tympanostomy tubes, ventilation tubes.

INTRODUCTION

Internationally, of all ventilation tubes used the majority are of the Shepard pattern, and this represents 57% of the various patterns in current use in Australia (Richards Medical Co [Australia], personal communication, 1989). It is difficult to obtain accurate figures of overall ventilation tube use. Information obtained from the Australian Commonwealth Department of Health (personal communication, 1989) for the 12 months ending 1988 reveals that a total of 43,376 ventilation tubes were inserted in private practice (2.63 per 1,000 population). Data given on market evaluations from a major manufacturer of ventilation tubes for the same period estimate 57,235 tubes were inserted in public and private practice; this number represents 3.46 per 1,000 population (Richards Medical Co, personal communication, 1989).

The Shepard ventilation tube has an internal diameter of 1 mm. Most otolaryngologists are familiar with its characteristic shape (Fig 1A) and the relatively shallow curve at the neck of the tube. The collar-button or Sheehy style ventilation tube, on the other hand, is a larger tube with a larger lumen of 1.25 mm diameter (Fig 1B). The collar-button style ventilation tube has wider flanges set at right angles to the lumen of the tube.

This study was designed to assess the proposition that some ventilation tube patterns less commonly used, notably the Sheehy or collar-button style tube, had a slower extrusion from the tympanic membrane when compared to the Shepard design in popular use.

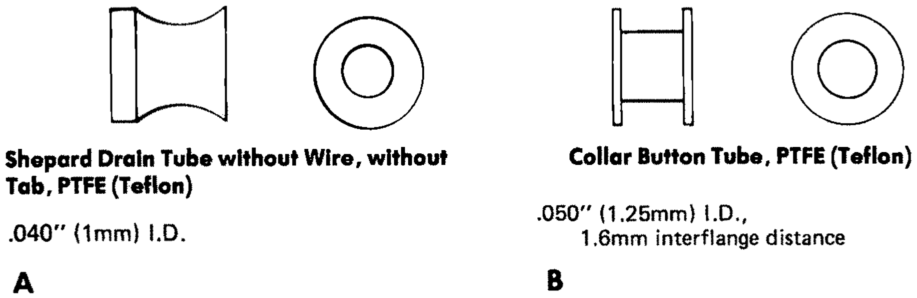
METHOD

The overall study consisted of 88 children who required bilateral ventilation tubes. The indications for insertion of tubes were chronic secretory otitis media and, less often, recurrent otitis media. Since one would expect the disease to be random in its severity on each side, a collar-button tube was usually inserted in the right tympanic membrane and a Shepard pattern inserted in the left tympanic membrane. Both tubes were placed anteriorly, and the patients were reviewed every 3 months for inspection of the tubes. The author had opportunity to review the patients in the series on occasion because of otologic symptoms other than the routine check of the ventilation tube. The first checkup on which the tube was noted to have been clearly extruded was taken as the point in determining the period of intubation. Identical criteria for definition of tube extrusion were used for both tubes, ie, the entire medial flange of the tube was seen to be out of contact with the tympanic membrane and lying free on the external auditory meatus. All periods specified relate to functioning ventilation tubes. By use of this method the period of intubation could be ascertained.

RESULTS

The two population histograms (Fig 2) demonstrate the range of intubation of the two ventilation tube styles.

The scatter diagram (Fig 3) displays the raw data. Each point represents a child plotted according to the period of intubation of the child's Sheehy and



Shepard Drain Tube without Wire, without Tab, PTFE (Teflon)

.040" (1mm) I.D.

A

Collar Button Tube, PTFE (Teflon)

.050" (1.25mm) I.D.,
1.6mm interflange distance

B

Fig 1. Ventilation tubes. A) Shepard. B) Collar-button.

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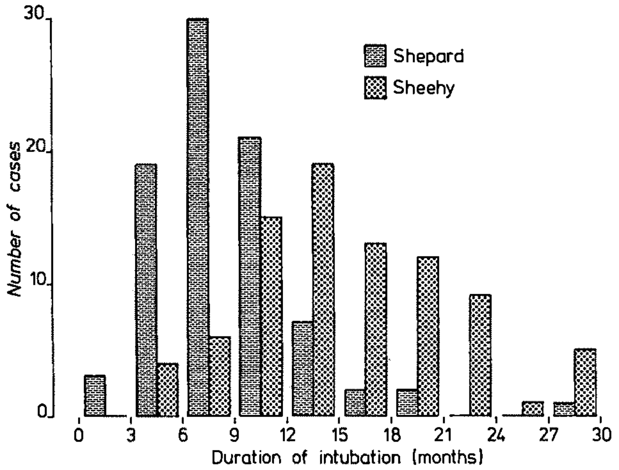

Fig 2. Histograms of two ventilation tube groups.

Shepard ventilation tubes. These points represent the absolute period of intubation (ie, until the point of extrusion) that could be best determined by the specific review described above. One would expect that if there was no difference between the tubes most points would be scattered around the line of gradient 1.0. However, it can be seen from Fig 3 that most patients are scattered around a line representing the calculated mean intubation ratio (collar-button/Shepard) of 2.05. That is to say, the collar-button tube stayed in place about twice as long as the Shepard.

By subjecting the results to statistical analysis with the t test a value is obtained that exceeds the probability level of 0.1% and is therefore highly significant.

DISCUSSION

Since the two different styles of ventilation tubes were used in each child with bilateral disease, the study validly shows a twofold difference in intubation time in favor of the collar-button or Sheehy style of tube.

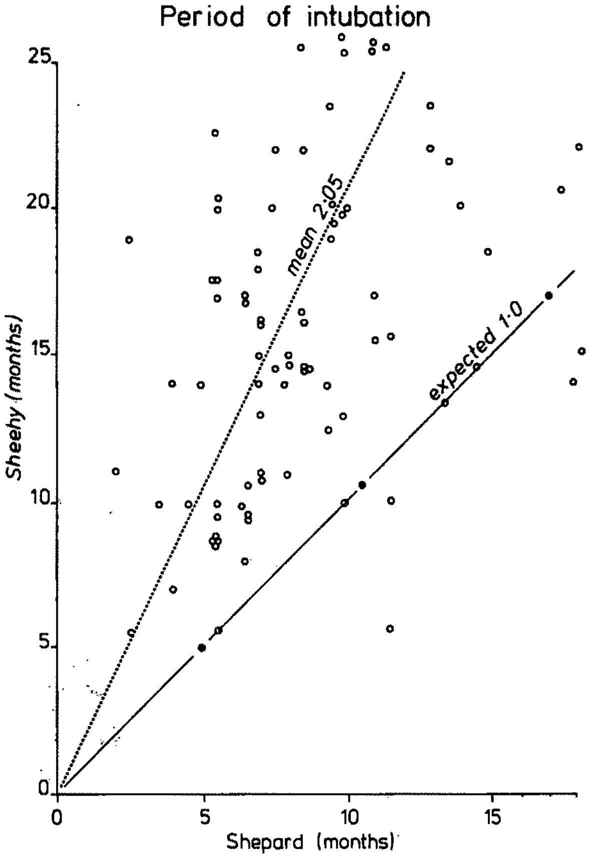

Fig 3. Scatter diagram showing duration of Sheehy collar-button versus Shepard ventilation tubes.

Although there are few studies to imply that better results in the treatment of chronic secretory otitis media can be expected with longer intubation with ventilation tubes,[1] the collar-button or Sheehy style tube merits consideration for use in the child with recurrence of chronic secretory otitis media after the use of tubes, in whom a longer period of intubation may be desirable.

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RESULTS OF MICROVASCULAR DECOMPRESSION OF THE EIGHTH NERVE AS TREATMENT FOR DISABLING POSITIONAL VERTIGO

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A total of 41 patients who underwent microvascular decompression to relieve disabling positional vertigo in one 12-month period were studied. At follow-up examinations 2½ to 3½ years after the operation, 30 patients had total relief of their symptoms or were considerably improved, to the point that they could resume normal work or other activities in which they were not able to engage before the operation. Two of the 41 patients had mild improvement, and the final 9 patients had no change in their symptoms. One patient, who had had a previous vestibular nerve section without improvement, underwent microvascular decompression of the stump as well as decompression of the opposite side with no relief; 3 of these 9 patients had clear signs of bilateral vestibular nerve compression, but elected not to undergo a second procedure at that time. One patient lost hearing as a result of the operation, and 1 who had a second operation suffered a hearing loss and subsequently underwent vestibular nerve section with improvement of the symptoms. Two patients had transient deficits related to cranial nerves IV and X. The remaining patients had no complications from the operation.

KEY WORDS — disabling positional vertigo, microvascular decompression.

INTRODUCTION

Disturbances of the vestibular system can cause a variety of symptoms and signs, depending on the site of lesion and the nature of the lesion. The best-described of such disorders is Meniere's disease, which has been the subject of numerous studies. The symptoms of Meniere's disease are generally believed to result from a disturbance in the balance of pressures in the different fluid compartments of the inner ear. However, the exact cause of these disturbances is so far unknown.

In contrast to Meniere's disease, which has a well-defined triad of symptoms, we have described a disease entity we call disabling positional vertigo (DPV) that is characterized by more or less constant vertigo and a sensation of being off balance, and that is associated with persistent nausea.[1] The onset of these symptoms is usually sudden and occurs early in life. The symptoms typically worsen over time, and spontaneous remissions are rare. Further, the symptoms of DPV are resistant to conventional treatments for vestibular disorders. For example, physical exercise and medications to suppress vestibular function not only have no beneficial effect on DPV — they often make the DPV symptoms worse. The only medication that has been shown to decrease the severity of the symptoms in patients with DPV is diazepam. Over time, patients with DPV frequently develop symptoms from adjacent cranial nerves VII and V and of the nervus intermedius; they may also experience a slowly progressing hearing loss[2] and/or tinnitus.

The symptoms of DPV suggest that the site of the lesion is the vestibular nerve rather than the end organ (labyrinth). This hypothesis is supported by the finding that these symptoms can be effectively alleviated by microvascular decompression (MVD) of the intracranial portion of the eighth nerve.[1-3] Other investigators (ie, McCabe and Gantz[4]) have presented radiographic evidence that unusual vascular loops may occur around the intracranial portion of the eighth nerve, and they have postulated that these loops cause the symptoms of DPV. These loops are different, however, from the loops that McCabe and Harker[5] described as entering the internal auditory meatus.

We describe the results of MVD of the eighth nerve in all 41 patients with DPV (32 women and 9 men) who were operated upon at our institution in one 12-month period. This paper describes these patients' results 2½ to 3½ years after the operation.

METHODS

Patients were selected for MVD when they fulfilled the criteria described previously.[2,3] Briefly, this selection was based mainly on case history and symptoms, and on evaluation of brain stem auditory evoked potential (BAEP) recordings and audiometric and vestibular tests. In the selection of patients for operation, greater emphasis was placed on case history and BAEP test results than on other tests. All patients had undergone more than one computed tomographic scan and/or magnetic resonance imaging procedure, and results of all such procedures were normal. Usually, patients older than 70 years were not operated on because of their higher risk of complications from the operation and anesthesia.

The following audiometric tests were used in determining if the eighth nerve was involved in the patients' symptoms.

Audiometry. Pure-tone and speech audiometry

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were carried out by use of conventional, high-quality equipment and recorded speech material. The tests were performed in a sound-insulated booth by a certified audiologist. In setting up our diagnostic criteria for patients with suspected DPV, we used our findings from patients with hemifacial spasm (HFS).

As we previously reported,[6] some patients with HFS had unusual notches in the middle frequency range (11%). These notches did not involve the 3- to 4-kHz range. In addition, 12% of patients with HFS had an up-sloping, low-frequency hearing loss resembling that seen in early stages of Meniere's disease; however, none of the patients with HFS had vertigo or fluctuating hearing loss. We interpreted these changes in the pure-tone audiograms to be caused by a selective insult to the eighth nerve; specifically, a blood vessel was compressing the facial nerve and causing the patient's HFS.

In patients with vertigo we have regarded a notch of 15 dB over one octave as indicative of vascular compression of the eighth nerve. A low-frequency hearing loss of 25 dB or more at 500 Hz in patients who had normal middle ear function (normal tympanograms) was likewise regarded as an indication of eighth nerve disease.

Tympanometry. Tympanometry was performed with standard equipment.

Acoustic Middle Ear Reflexes. The reflex responses to contralateral stimulation with pure tones at frequencies of 500, 1,000, and 2,000 Hz were recorded. A threshold elevation (threshold greater than 95 dB) in patients with normal middle ear pressure as judged from the tympanogram was taken as a sign of involvement of the eighth nerve.[7]

Brain Stem Auditory Evoked Potentials. The BAEPs were obtained in response to 2-kHz tonebursts (1-millisecond duration, random phase) presented at a rate of 10/s through miniature stereo earphones at a peak sound pressure level of 95 dB. The potentials were recorded differentially between the forehead and the ipsilateral mastoid, averaged (256 data points at a 40-microsecond sampling interval), and filtered with zero-phase digital filters.[8] Computer programs automatically printed the latency values of the various peaks. Two consecutive runs of 4,096 responses were done on each ear.

A difference in the interval between peaks I and III (interpeak latency [IPL]) of 0.2 millisecond between the two sides was taken as an indication of involvement of the eighth nerve on the side with the longest IPL I-III. If the amplitude of the BAEP was considerably lower on one side (less than one third that on the other side), then this finding was also taken as an indication of involvement of the eighth nerve. In addition, a difference in IPL III-V of 0.2 millisecond between the two sides was taken to indicate lateral brain stem compression contralateral to the side with the longer IPL. (Peak V is regarded to be generated by contralateral structures of the ascending auditory pathway.[9]) In addition, absolute values of IPL I-III exceeding 2.3 milliseconds and of IPL III-V exceeding 2.2 milliseconds in patients with normal pure-tone audiograms were regarded as abnormal. If this finding occurred on both sides, it was taken as a strong indication of bilateral involvement of the eighth nerve.

Vestibular Tests. Standard vestibular tests were performed at the Eye and Ear Hospital of Pittsburgh's Balance Disorder Center and interpreted by the physician in charge of that laboratory.

Bilateral involvement of the eighth nerve was indicated by bilateral BAEP changes and/or bilateral threshold elevation (or absence) of the middle ear reflex. In addition, signs of bilateral involvement of cranial nerves that are adjacent to the eighth nerve were taken as strong indications of bilateral compression of the eighth nerve and, thus, bilateral DPV.

Audiometric tests, including recording of BAEPs, were performed prior to the operation and at least twice postoperatively: on the patient's last day in the hospital (usually 6 days postoperatively) and 3 months after the operation. Audiometric tests were repeated at regular intervals thereafter. Vestibular testing was done prior to the operation and, if indicated, repeated 1 year after the operation.

Table 1 summarizes clinical data, symptoms from adjacent cranial nerves, and results of audiovestibular tests for the 41 patients in this study.

The Figure[8] shows the results of audiometric testing and BAEP recording in a patient with DPV on the right side.

Of the 41 patients in this study, 5 had previously had a similar MVD operation on the opposite side performed at our institution, and they were now undergoing a second MVD operation because of signs and symptoms of bilateral involvement. Three patients in this study underwent the second operation to relieve persistent symptoms. A fourth patient had undergone vestibular nerve section at another institution and had bilateral MVD operations during the study (Table 2).

The MVD method has been described in detail previously.[1] A retromastoid craniectomy is performed to reach the intracranial portion of the eighth nerve. This is similar to the procedure used to treat other vascular compression syndromes such as trigeminal neuralgia and HFS.[10,11] Vascular compression is relieved by placing shredded Teflon felt between the vessel and the nerve. Auditory evoked potentials are monitored intraoperatively in all cases to reduce the risk of hearing loss.[12,13]

TABLE 1. SUMMARY OF CLINICAL DATA FROM 41 PATIENTS OPERATED ON FOR DISABLING POSITIONAL VERTIGO

Pt No.	*Sex*	*Age (yr)*	*Duration of Symptoms (yr)*	*Auditory Test Results* *AA*	*AR*	*BAEP*	*Vest*	*Additional Symptoms*	*Side of Operation*	*Positive Case History*
1	F	61	2			+	+	Ear pain (L), V, V1, V2 numbness	L	+
2	F	32	4		+	+	+	VII twitch	L	+
3	F	35	5	+	+	+	+		L	+
4	F	57	8			+	+	Ear pain (R)	R	+
5	F	63	7	+		+	+	Aural fullness (R)	R	+
6	F	52	4	?	+	+	+	V, V3	L	+
7	F	41	5	+		+	+	V numbness	L	+
8	M	42	18	+		+	+		L	+
9	F	30	8 mo	+			+	Ear pain (R)	R	+
10	M	52	20	+		+	+		R	+
11	F	55	15			+	+		L	+
12	F	53	9	+	+		+	VII twitch	R	+
13	F	50	8	+			+	Ear pain (R)	R	+
14	F	32	4			+	+	Ear pain (R)	L	+
15	F	37	8				+	Ear pain (R)	R	+
16	F	43	4	+	+	+	+		R	+
17	F	53	2	+		+	+		R	+
18	F	64	4	+	+	+	+	V, V1 pain	R	+
19	F	54	1	+		+	+	V numbness	R	?
20	F	46	8	+			+	Ear pain (L)	L	+
21	M	42	1.5	+	+	+	+	VII twitch	R	
22	F	56	20		+	+	+	Ear pain (L), V (R)	L	+
23	F	47	2			+	+		R	
24	F	60	1.5	+		+	+		L	+
25	M	28	1.5	+			+	Aural fullness	R	+
26	F	52	4	+		+	+	V, V1, VII twitch	L	+
27	M	54	6	+	+	+	+		R	+
28	F	29	7	+		+		Ear pain (L)	L	+
29	M	37	6	+	+	+	+		R	+
30	F	52	17		+	+	+		L	+
31	M	34	4	+		+	+		R	+
32	M	46	18			+	+	VII bilateral twitch	L	
33	F	35	10	+	+	+	+	VII twitch, V numbness	R	+
34	F	31	20			+			R	
35	F	53	6	+	+	+	+		R	+
36	F	32	4			+	+		R	+
37	F	39	5	+	+	+		VII twitch	R	+
38	M	37	5			+		VII twitch	R	+
39	F	63	5	+		+	+	Ear pain (L)	L	+
40	F	43	3		+	+	+	Ear pain (R)	R reop	+
41	F	32	5	+	+	+		V, V2, ear pain	L reop	+

Pluses indicate abnormal test results.

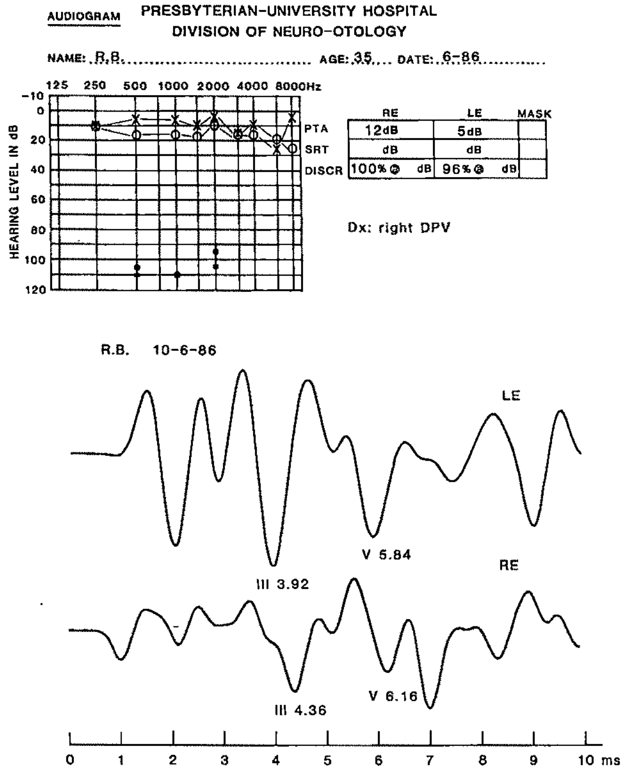
AA — pure-tone and speech audiometry, AR — acoustic middle ear reflex response, BAEP — brain stem auditory evoked potentials, Vest — vestibular tests, V — fifth cranial nerve (trigeminal nerve), VII — seventh cranial nerve (facial nerve), reop — reoperation.

RESULTS

In one 12-month period, about 200 new patients were seen in our clinic with symptoms of vestibular disturbances, 41 of whom were selected for operation. Of these 41 patients, only 4 had been employed prior to the operation; the other 37 had been unable to work because of the severity of their DPV symptoms. About half of the patients were confined to their houses or had to use a wheelchair for transportation and cooking and other chores.

During the 2½ to 3½ years after the operation, 30 patients either became totally symptom-free or had such significant improvement in symptoms that they could return to work or meaningful activities full-time (Table 2). Two of the patients who were operated on experienced some improvement, but by their own subjective evaluations experienced only minor relief of symptoms. Finally, 9 patients experienced no noticeable improvement after the operation. Of these 9, 3 had clear signs of bilateral involvement but elected not to have an operation on the other side during the time of the present study; 2 of them underwent a second MVD later on the same side, and 1 of these improved. One patient had undergone a vestibular nerve section previously at another institution. This patient had no relief from MVD of the vestibular nerve stump or from MVD on the opposite side.

All of the patients who were operated on clearly had significant compression of the eighth nerve by



(Case 33) Results of audiometry, recording of acoustic middle ear reflex responses, and brain stem auditory evoked potential testing in patient with disabling positional vertigo (DPV) on right side of 10 years' duration. Auditory evoked potentials are shown with vertex positivity as downward deflection and after averaging and digital filtering.[8] Dx — diagnosis.

one or more vessels. The vascular compression that was identified at the time of operation varied from severe (grooves clearly evident in the vestibular portion of the eighth nerve) to moderate. In many cases, multiple vessels were found compressing the intracranial portion of the eighth nerve. Frequently, the offending vessel was located under the flocculus, which then had to be dissected from the eighth nerve in order to move the compressing vessel off the nerve. In most cases the offending vessels were arteries, but veins were found to compress the nerve in several of these patients.

One of the 41 patients suffered a complete loss of hearing as a complication of the operation, and one patient suffered a hearing loss following a second operation. This patient subsequently underwent vestibular nerve section with improvement of vertigo. One patient had temporary vocal cord paralysis (cranial nerve X), and one patient had paralysis of the superior oblique muscle (cranial nerve IV), but these deficiencies resolved completely by 2 to 4 months after the operation. There were no other complications related to the operations.

In all three patients who were operated upon for the second time, additional vascular compression was found.

DISCUSSION

The results of the present study show that MVD is an effective way to treat patients with DPV.

Evaluation of treatments for vestibular disorders is hampered by the fact that there are relatively few objective tests of patients' functional capacities. That is, objective tests of nerve function correlate poorly with patients' subjective perceptions of their situation. We have therefore elected to use the patients' own evaluations of their conditions and their descriptions of which activities they are able to perform on a regular basis as outcome criteria. For example, we assume that the treatment has been effective for a patient who was unable to work or perform ordinary household chores or drive before the operation and who can do so postoperatively. Patients who had been confined to bed for a greater part of each day for several years preoperatively and who postoperatively can carry out such tasks as shopping, social activities, and moderate garden work are considered to have improved as a result of treatment, but not to be cured.

While MVD to relieve trigeminal neuralgia and HFS usually results in immediate or almost immediate total relief of symptoms, MVD to treat DPV usually results in gradual improvement in symptoms over 4 to 12 months. The first symptom that disappears is always nausea. Then, vertigo gradually decreases from constant to fluctuating and then slowly decreases in intensity before it totally disappears. Patients with a long history of DPV (longer than 10 years) generally recover more slowly than do those who have had DPV for a shorter period before the operation, and patients with a long history of DPV often do not experience complete resolution of their symptoms. In this respect, DPV is similar to trigeminal neuralgia — patients who have had trigeminal neuralgia for a long time before MVD often do not become pain-free until long after the operation.

The follow-up period for patients in this study is too short to permit any definite conclusions to be drawn regarding recurrence of DPV after MVD. However, the first patients who were operated upon by MVD in our institution have now been followed for almost 8 years, and we have not seen any recurrences of DPV in patients who had significant improvement after the operation.

A complicating factor in the selection of patients for MVD is related to determination of site of lesion. In our experience, radiographic techniques such as air cisternography can reveal vascular loops in the cerebellopontine angle, but not with sufficient resolution to permit us to determine if a vascular loop is in contact with the eighth nerve or only close to the eighth nerve. Since it appears that only vessels in firm contact with the nerve cause disturbances in vestibular function, this is a critical factor. The results of intraoperative electrophysiologic

TABLE 2. SUMMARY OF OPERATIVE FINDINGS, RESULTS, AND COMPLICATIONS IN 41 PATIENTS OPERATED ON BY MICROVASCULAR DECOMPRESSION OF THE EIGHTH NERVE

Pt No.	*Operative Findings*	*Results*	*Complications*	*Comments*
1	AICA at BS	30% Improved		
2	Pontomed vein grooving	Excellent	Superior oblique paresis, resolved	Endolymphatic shunt (R) in 1984
3	Vein grooving	Excellent		Tinnitus decreased
4	AICA and pontomed vein	Excellent		
5	AICA and vein	Excellent		Occasional lightheadedness
6	AICA and vein	Improved, then no change		Stapedectomy x2 (L) in 1982
7	AICA and pontomed vein	Excellent		
8	AICA grooving at BS	Excellent		
9	AICA between VII and VIII	Excellent		
10	AICA grooving	No change		Reop (L, R) in 1988, improved
11	AICA grooving and pontomed vein	Excellent		
12	AICA and PICA grooving	No change	Hearing loss	
13	AICA grooving	Excellent		
14	PICA and vein grooving Reop, small artery and vein	Slight improvement Improved		
15	AICA and pontomed vein	Slight improvement		Reop (R) in 1988
16	AICA grooving and vein	Excellent		
17	AICA grooving	Excellent		
18	AICA and veins	Improved		Reop 1988, excellent
19	Pontomed vein	Excellent		
20	AICA, PICA, and vein	Improved, then no change		
21	Pontomed vein	No change		Bilateral symptoms
22	AICA, PICA, and vein	Improved		Bilateral symptoms
23	AICA grooving	Improved		
24	AICA and veins	Excellent		Onset after MVA
25	Vein grooving	Improved		Operation (L) in 1988
26	AICA	Improved		Operation (R) in 1984
27	Vertebral artery at BS Reop (L), pontomed vein	No change No change		VNS (L) in 1985
28	AICA and PICA loops	Improved		Operation (R) in 1987, excellent
29	Large vein at BS	Excellent		Improved hearing
30	AICA and vein	Excellent		
31	AICA and PICA	No change		Onset after MVA, bilateral symptoms
32	AICA and pontomed vein	Improved, then no change		Bilateral symptoms
33	AICA and vein	Excellent		
34	PICA and pontomed vein	Improved, then no change		Basilar artery migraine?
35	AICA and pontomed vein	Excellent	Vocal cord paresis, resolved	
36	AICA grooving	Improved		Operation (L) in 1988
37	AICA loop	Excellent		
38	Multiple veins	Excellent		
39	PICA and vein	Excellent		
40	Reop, Teflon slipped	Improved	Hearing loss	VNS (R) in 1987
41	Reop, small vein and artery	Improved		

AICA — anterior inferior cerebellar artery, BS — brain stem, pontomed — pontomedullary, PICA — posterior inferior cerebellar artery, Reop — reoperation, MVA — motor vehicle accident, VNS — vestibular nerve section.

studies have shown that blood vessels only fractions of a millimeter in diameter can cause HFS, while larger arteries and veins may not play any role in causing HFS.[14] We have the impression that a small vessel (or vessels) can cause DPV, although we do not have intraoperative electrophysiologic methods to prove it.

Because only one of the patients operated on during the period covered by this study had previously undergone vestibular nerve section, no conclusions can be drawn about this procedure and the lack of success of MVD in relieving this patient's symptoms. However, Kim and Fukushima[15] showed that previous destructive procedures decrease the success rate of MVD in patients with HFS. In an unpublished study of six patients with DPV who had undergone previous vestibular nerve section, we found that MVD of the eighth nerve had no beneficial effect. Thus, the poor results of MVD in the one patient in the present study who had undergone nerve section previously are not surprising.

ACKNOWLEDGMENT — The author is grateful to Peter J. Jannetta, MD, for making patients under his care available for this study.

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Ann Otol Rhinol Laryngol 99:1990

EXPERIENCE WITH THE WILKIE PROCEDURE FOR SIALORRHEA

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Sialorrhea (drooling) is most commonly seen in children with cerebral palsy or mental retardation. Surgical procedures for the control of sialorrhea include salivary gland excision, parasympathetic nerve section, and salivary duct ligation and/or rerouting. Eighteen children between the ages of 5 and 17 years underwent bilateral submandibular gland excision and rerouting of Stensen's duct (Wilkie procedure). All children had severe drooling associated with cerebral palsy or mental retardation. Follow-up at 7 years showed satisfactory control of sialorrhea in 16 of 18 patients (89%). There was one major complication: xerostomia. Our results indicate that submandibular gland excision together with parotid duct retropositioning provides effective control of sialorrhea in most cases. Unfavorable head and mandibular posturing seemed to cause persistent sialorrhea in one case.

KEY WORDS — cerebral palsy, mental retardation, parotid duct, salivary gland, sialorrhea, submandibular gland, Wilkie procedure.

INTRODUCTION

Sialorrhea (drooling) is commonly seen in children with cerebral palsy or mental retardation. It is a debilitating handicap causing severe social and nursing problems. The impact of drooling on the child and his peers should not be underestimated. This study presents our results in managing these functional derangements.

The pathophysiology of drooling in the brain-damaged child involves disturbances in the oral and pharyngeal parts of the swallowing mechanism that are associated with generalized muscular spasticity.[1,2] Pathologic tongue movements, an uncoordinated pharyngeal sphincter, and circumoral spasticity are common findings.[2] Tongue thrusting may lead to malocclusion, especially open-bite deformity, further impeding function. As a result of these factors, the swallowing mechanism fails to clear saliva from the anterior portion of the oral cavity into the posterior oropharynx, and drooling results.

Normal salivary secretion is 1 to 1.5 L/d. Ninety percent of salivary flow is contributed by three pairs of major salivary glands (parotid, submandibular, and lingual). As much as 70% of the resting salivary flow originates in the submandibular glands alone.[3] Any surgical procedure, to be effective in controlling sialorrhea, must include the submandibular glands. Their removal alone diminishes the salivary flow significantly.

The salivary flow from the major glands is dependent upon parasympathetic innervation, which is mediated by acetylcholine. Parasympatholytic medications have been advocated to control drooling. Unfortunately, the dosage needed to obtain a therapeutic response often causes significant systemic effects. Alternatively, surgical interruption of parasympathetic secretomotor innervation to the major glands has been proposed. The middle ear provides a common access to the chorda tympani and Jacobson's nerves — the parasympathetic innervation to the submandibular and parotid salivary glands. Parasympathetic denervation, although relatively easy to perform by a simple transtympanic approach, carries only a 50% long-term control rate.[4]

Other surgical approaches have been employed for the treatment of drooling. These include excision of the submandibular glands, ligation of the salivary gland ducts, retropositioning of Wharton's or Stensen's ducts, and various combinations of the above.

In 1967 Wilkie[1] described a procedure for the control of sialorrhea that consisted of the excision of the submandibular glands and the rerouting of the parotid ducts into the tonsillar fossae. Since 1981 this procedure has been employed in our patient population.

METHODS

Eighteen patients, 5 to 17 years of age (average, 9½ years), were operated on for drooling at the Kaplan Hospital, Rehovot, Israel, between 1981 and 1988. All patients had severe drooling associated with cerebral palsy (17) or mental retardation (1). None of the patients were institutionalized. In all cases physiotherapy was attempted prior to surgical therapy.

Patients were selected for operation on the basis of the severity of drooling and its sequelae and of

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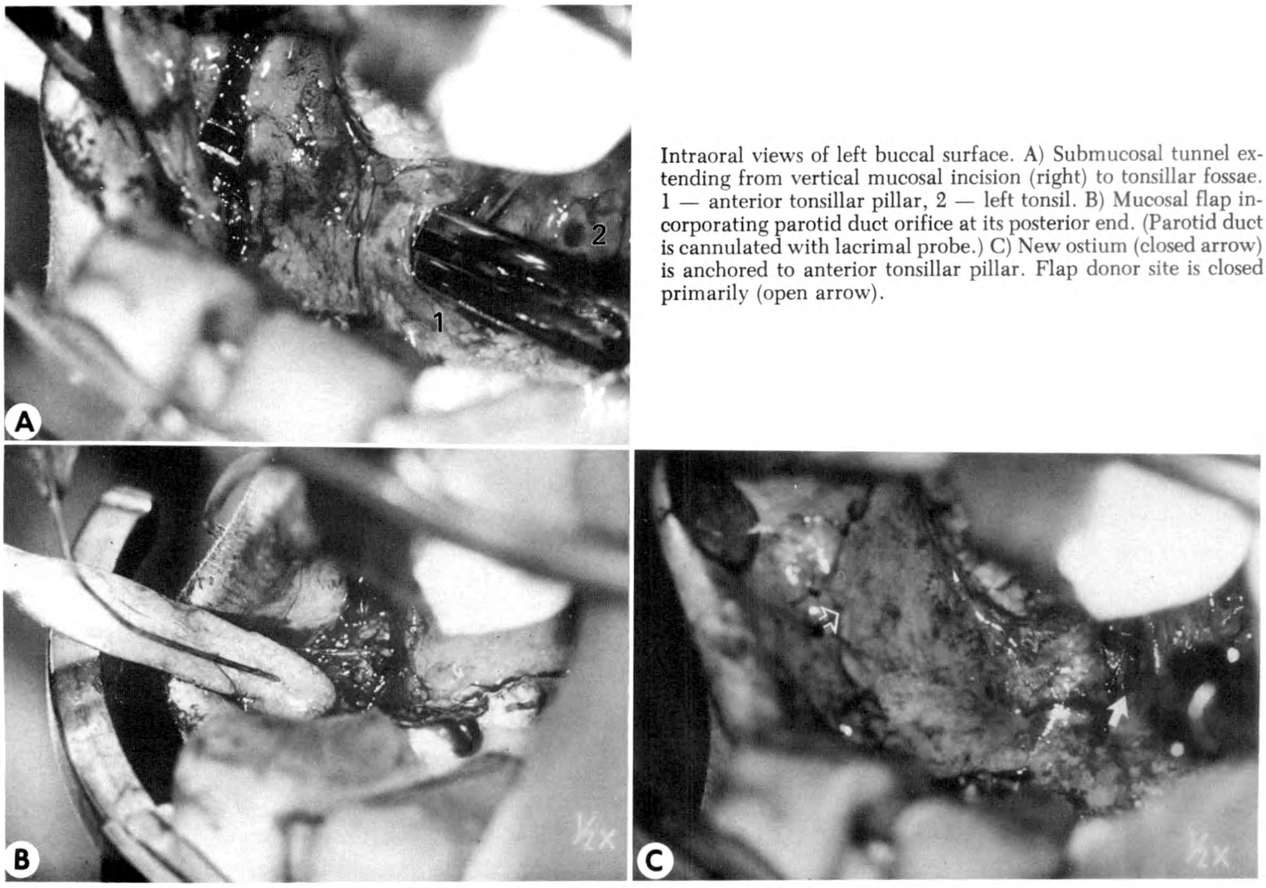

Intraoral views of left buccal surface. A) Submucosal tunnel extending from vertical mucosal incision (right) to tonsillar fossae. 1 — anterior tonsillar pillar, 2 — left tonsil. B) Mucosal flap incorporating parotid duct orifice at its posterior end. (Parotid duct is cannulated with lacrimal probe.) C) New ostium (closed arrow) is anchored to anterior tonsillar pillar. Flap donor site is closed primarily (open arrow).

the parents' motivation for surgical therapy. The severity of drooling was qualitatively assessed from detailed histories obtained from the patients' parents and by physical examination. Factors that had bearing on the severity of drooling included nursing problems, psychosocial factors, and motivation for surgical treatment. Any factors contributing to upper airway obstruction, such as tonsillar and adenoidal hypertrophy, were identified and treated prior to operation for drooling. Two patients required tonsillectomy before undergoing operation for drooling. Operation was delayed until the patients were 5 years of age, because drooling tends to improve in early childhood.

Operative Technique. The operation was performed under general anesthesia with orotracheal intubation. The submandibular salivary glands were excised in the usual fashion with an upper cervical incision. The oral cavity was then exposed by means of the Dingman mouth gag. The parotid duct orifice was identified opposite the second upper molar. The anterior tonsillar pillar was identified, and the distance between it and the parotid duct was measured. This provided an estimate of the mucosal flap length required for retropositioning of the parotid duct. A vertical incision was then made through the mucosa and submucosa 2 to 3 mm posterior to the parotid duct orifice. Through this incision, a submucosal tunnel was bluntly dissected to a point immediately posterior to the anterior tonsillar pillar (see Figure, A). The plane of dissection was superficial to the pterygomandibular ligament and deep to the palatoglossus muscle. Once an adequate tunnel had been obtained, attention was directed to the creation of a mucosal flap that incorporated the orifice of the parotid duct. A rectangular, 1-cm-wide horizontal (or vertical) mucosal flap was outlined, extending 2.5 to 3 cm anterior (or caudal) to the parotid duct orifice. The parotid duct was cannulated with a lacrimal probe and the flap was developed, incorporating the duct at its posterior end (see Figure, B). The distal portion of the parotid duct was mobilized to permit posterior displacement, and the flap was tubed on the lacrimal probe to create an extension to the parotid duct. The tube was secured with interrupted chromic sutures. The tubed flap was rotated posteriorly through the previously made submucosal tunnel and anchored just to the anterior tonsillar pillar (see Figure, C). By use of upper and lower "guide" sutures, care was taken not to twist the tube. The extended ostium of the tube was secured in the tonsillar fossa with interrupted sutures. The flap donor site was closed primarily.

Patients were maintained on intravenous hydration until oral fluids were tolerated. There was usually moderate facial swelling that resolved in a few days. Most patients were discharged by the fourth postoperative day.

RESULTS

Operative results were assessed at a follow-up of 3 months to 7 years (mean, 3½ years). The procedure was considered a success if sialorrhea was controlled and no signs of xerostomia were present on physical examination. Sixteen of the 18 patients (89%) had good control of sialorrhea.

One failure was due to excessive mouth dryness in a 7-year-old child who had minimal brain damage without muscle spasticity. Another failure was due to persistent sialorrhea in a patient with severe spastic quadriplegia. This patient had a constant flexed head posture secondary to cervical spine contracture. Drooling was aggravated in this case by the effect of gravity.

Postoperative complications included intraoral sialocele requiring marsupialization in one case, and transient recurrent parotid swelling in another.

DISCUSSION

Several surgical procedures have been used to control sialorrhea over the past two decades: transtympanic parasympathetic nerve section, submandibular duct rerouting as a single procedure or together with parotid duct ligation, parotid duct ligation alone, and submandibular gland excision.[4-12] Excision of submandibular salivary glands and parotid duct retropositioning as first reported by Wilkie[1] has achieved good overall results when followed long-term in a large series of patients (86%).[13]

The excision of the submandibular salivary glands eliminates their major contribution (70%) to the resting salivary flow. Retropositioning of the parotid ducts diverts most of the remaining salivary flow from the overloaded anterior portion of the oral cavity into the posterior oropharynx, where it is required to be for swallowing. Together, these changes effectively cope with the underlying pathophysiology of drooling. Our control rate (89%) is similar to that first reported by Wilkie and Brody.[13] A similar control rate (86%) was recently reported by Brundage and Moore[11] for submandibular gland resection and parotid duct ligation. However, for this procedure to be effective, atrophy of the parotid gland must occur.

Careful selection of cases is critical. The procedure is relatively radical and carries the risk of dry mouth. It should therefore be confined only to those patients with severe drooling that has significantly handicapped their quality of life. The patient's head and mandibular posture is an important prognostic finding to be considered preoperatively. Patients with severe spasticity may occasionally have unfavorable head or mandibular postures such as a flexed head or open bite deformity. In these cases, gravity interferes with salivary clearance and aggravates drooling. The already compromised swallowing mechanism is further challenged by the effect of gravity. Even Wilkie's procedure might not be successful in this group of patients. We feel that one of our patients failed because of this factor.

To conclude, the Wilkie procedure is an effective means of controlling sialorrhea in children. It has a low rate of complications and is based on sound physiologic principles.

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Ann Otol Rhinol Laryngol 99:1990

INNER EAR DECOMPRESSION SICKNESS COMBINED WITH A FISTULA OF THE ROUND WINDOW

CASE REPORT

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Inner ear barotrauma with rupture of the round or oval window secondary to diving and decompression sickness (DCS) of the inner ear can be a difficult diagnosis to differentiate. The dive profile or associated elements of DCS will often confirm the diagnosis. Occasionally, diagnosis is made during recompression or during operation. The differential diagnosis is important, since immediate recompression is indicated for inner ear DCS, while it is contraindicated in cases of inner ear barotrauma. We have found no cases reported in the world literature in which both diseases have been diagnosed and proven simultaneously. We present a case of a diver who developed DCS with inner ear manifestations complicated by a round window fistula. Treatment and clinical outcome are discussed along with a brief review of the suspected cause.

KEY WORDS — decompression sickness, diving, fistula, inner ear, round window.

INTRODUCTION

Inner ear decompression sickness (DCS), historically referred to as "staggers" because of the disruptive effects on the vestibular apparatus, has been recognized since the early days of caisson work. Described by Jaminet[1] in the late 19th century, it is felt to be a relatively uncommon manifestation of central nervous system (CNS) involvement. Symptoms of this disease include hemorrhage, tinnitus, deafness, vertigo with dysequilibrium, nausea, and vomiting. Examination may reveal nystagmus. The cochlea, the vestibule, or both may be involved, and symptoms of either the hearing or the vestibular system may predominate. Inner ear DCS is a true emergency and must be treated immediately to avoid permanent damage.

Ear problems related to compressed air exposures, including hearing loss, were described somewhat earlier. Almour[2] described an early report in 1820 of diving-related ear pain and a report by Smith in 1873 that gave the first detailed description of some of the otic lesions associated with compressed-air work. Boot,[3] in 1913, used the term "caisson workers' deafness" to describe the auditory loss — acute or chronic, temporary or permanent — following such exposures. Goodhill[4] discussed sudden deafness and round window ruptures in 1971; and in 1972, Freeman and Edmonds[5] recommended the term "inner ear barotrauma" to describe sensorineural deafness associated with diving in the absence of DCS. A variety of mechanisms have been proposed to explain this hearing loss, and the exact mechanism remains unclear.

Inner ear barotrauma can produce symptoms remarkably similar to those seen with inner ear DCS: hearing loss, vertigo with dysequilibrium, nausea, and vomiting. Farmer[6] highlighted a number of factors to be considered in the diagnosis. One is time of onset: symptoms appearing during compression are likely to be caused by inner ear barotrauma, whereas symptoms starting during or shortly after decompression are more likely attributable to inner ear DCS. Another is the dive profile, including the gas mixture used: shallow dives that do not approach decompression limits are unlikely to result in DCS. A history of rapid ascent or descent may be more likely to result in inner ear barotrauma, and most of these cases have been associated with air diving. The presence or absence of associated symptoms or physical findings will give an indication of whether the CNS is involved or whether the primary diagnosis is barotrauma.

The differential diagnosis, while sometimes difficult, is important. Farmer et al[6-8] stated that divers experiencing inner ear symptoms beginning during compression or after shallow dives in which DCS is unlikely should be suspected of having a round window rupture and should not be recompressed. Various authors,[8-11] on the other hand, have concluded that rapid recompression is required in cases of inner ear DCS to prevent permanent damage.

Edmonds et al[12] reported in 1974 that since 1970, it had been their policy to surgically explore the middle ears of divers having severe or progressive sensorineural deafness. Of the five patients examined, four were observed to have round window ruptures. These authors reported that hyperbaric oxygen therapy had been inadvertently or coincidentally administered in two of the cases of round window rupture, and that the treatment had no noticeable influence on either vestibular or cochlear function.

Parell and Becker,[13] in 1985, reported a case of a 38-year-old diver who presented with a 14-hour his-

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tory of hearing loss, constant sensation of spinning, and nausea after diving. He had exceeded the US Navy decompression limits by several minutes. He was slightly drowsy, with depressed psychomotor function. There was a left-beating spontaneous nystagmus with a pronounced rotatory component. Tandem gait was unsteady and Romberg's sign was positive. He was thought to have DCS, which was treated with a US Navy oxygen recompression table. Residual symptoms of dizziness and unsteadiness subsided over the following week. It was later postulated that nonotologic manifestations of his case may have been caused by fatigue, in that he had not slept for the 48 hours preceding presentation. The authors stated that the most likely alternative diagnosis was an inner ear fistula. They reviewed the literature and hypothesized three mechanisms for inner ear barotrauma: 1) hemorrhage within the inner ear, 2) labyrinthine membrane tear, and 3) perilymph fistula through the round or oval window.

When faced with a case of sudden hearing loss following diving, the clinician must evaluate the dive profile and consider the possibility of both DCS and inner ear barotrauma within the differential diagnosis. We present a case in which DCS, manifested by hearing loss, vestibular symptoms, and slurred speech, coexisted with a rupture of the round window, and discuss the treatment provided and the clinical outcome.

CASE REPORT

An experienced 45-year-old diver was referred from an area hospital following an evening dive to 20 m for 46 minutes. Shortly after surfacing, he experienced "dizziness" and nausea and "felt unwell." He noted the gradual loss of hearing in the right ear with a loss of balance, having a tendency to fall to the right side. These findings were verified on examination at the hospital, and he was noted, in addition to the more obvious otologic manifestations, to be slurring his speech, a finding verified by three separate health care workers. Despite the absence of overt signs of tympanic membrane involvement, he was felt to be a prime candidate for inner ear barotrauma. Because of the presence of signs suggestive of neurologic DCS, however, he was given 100% oxygen and referred to our office for evaluation. The differential diagnosis was inner ear barotrauma with round window rupture or DCS.

The patient arrived 1½ hours later complaining of dizziness, nausea, difficulty with balance, loss of hearing on the right side, and a feeling of unwellness. Examination revealed the following positive findings: Romberg's sign with immediate falling to the right side; marked reduction of hearing on the right side with bone conduction greater than air conduction by Rinne's test on the right; and localization of Weber's test to the left, suggesting a false-negative Rinne on the right side. There was a mild motor ataxia. A degree of past-pointing was present, finger manipulation was decreased in both accuracy and speed, heel-to-shin movement was performed with difficulty, and he was unable to perform a heel-toe walk. Mental ability was normal. Otoscopic examination revealed normal tympanic membranes, and further questioning failed to elicit significant history suggestive of inner ear barotrauma as the principal diagnosis. No nystagmus was present, and hearing on the left side was not appreciably impaired. Speech at the time of our examination was normal. The presence of nonotologic symptoms and the resolution, during transport, of the slurring of speech suggested that DCS was involved.

A trial under pressure was conducted at 9 m on 100% oxygen. This option was chosen, in part, to aid in the differential diagnosis of this patient but, more importantly, to avoid a further delay in treating what was suspected to be a serious form of DCS. Within 5 minutes he noted a distinct improvement in hearing, as well as a general feeling of well-being. He was further compressed to a depth of 18 m and continued on a Royal Navy treatment table 62. During the course of treatment, he noted a gradual increase in hearing to roughly 60% of the pre-dive level. He also noted the reduction, but not cessation, of nausea and dizziness. Speech remained normal. Clinical examination verified these subjective feelings with an increase of hearing on the right side and a significant reduction of lateralization on Weber's test. Upon surfacing he continued to complain of low-grade nausea, dizziness, and hearing loss. Romberg's sign had improved markedly, but remained positive to the right side. He remained unable to perform a heel-toe walk.

He was admitted to the hospital and referred for immediate otolaryngologic evaluation. An audiogram documented a significant hearing loss on the right side, and a lesser reduction at 4 kHz on the left (Fig 1). Romberg's sign remained positive and coordination remained reduced. Further recompression therapy was considered following the favorable response on initial treatment.

A second Royal Navy treatment table 62 was conducted 1 day after his initial treatment, with additional improvement in hearing and balance. Romberg's sign returned to nearly normal, but the patient remained unsteady while performing a heel-toe walk. He continued to complain of low-grade nausea and dizziness. Hearing improved to the 50% level, as documented by audiogram (Fig 2). It was felt at this point that no further benefit would be derived from additional recompression therapy, and he was considered for surgical exploration of the middle ear on the basis of his persistent symptoms and signs. He was taken to the operating room on the sixth day following the accident, and a par-

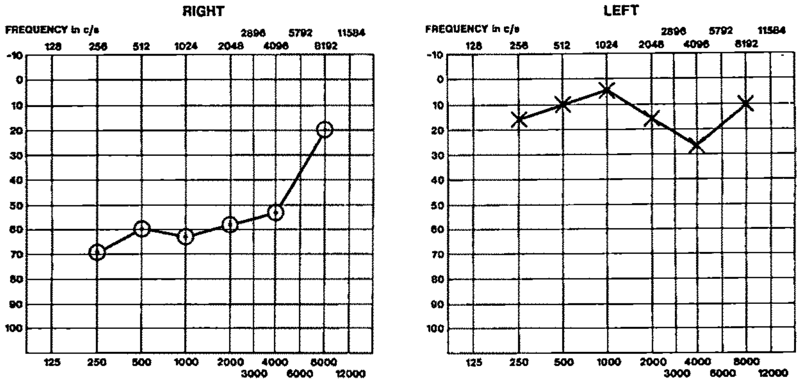

Fig 1. Initial audiogram, completed following first recompression treatment on June 30, 1988. (Bone conduction omitted for clarity.)

tially healed round window fistula was found and patched with a perichondral graft. A complete resolution of his nausea and dizziness was evident upon his recovery from anesthesia. Hearing increased to the 30% level (Fig 3). Romberg's sign returned to normal, and he was now able to perform a heel-toe walk without difficulty.

Additional clinical studies were performed in an effort to confirm the original diagnosis of DCS. Auditory and visual evoked brain stem responses were obtained; these were normal. On the 10th day following his dive the patient underwent an isotope brain scan utilizing ^{99m}Tc-hexamethylpropyleneamine oxime as described by Macleod et al[14] at the Undersea and Hyperbaric Medical Conference in June 1988. This scan showed a 3-cm area of ischemia across the auditory cortex on the right side and an area of ischemia in the left frontal lobe (Fig 4).

DISCUSSION

The Dive. A routine dive to 20 m for 46 minutes is at the edge of the no-stop limits of the British Sub-Aqua Club sport tables on which the man was diving. It is within the no-stop limits according to the US Navy air decompression limits, but by Royal Navy air diving tables, such an exposure requires a 5-minute stop at 3 m. It is well known that dives within the limits of a table may give rise to DCS, and factors outside the tables may also play a role.

The risk of developing DCS on any table appears to rise as age increases. The generally accepted age at which this risk rises notably is 40. This man, at 45, would carry an additional risk. There is no other evidence of unusual stresses commonly argued to add to the risk of DCS. While this was a night dive, he was not particularly fatigued, and he had no difficulty during the dive. He had not been drinking alcohol prior to the dive, was an experienced diver using his own gear, was a nonsmoker in reasonable physical condition, and was not overweight for his age at 175 cm and 72 kg. He was taking no medications and was diving at sea level without unusual weather conditions. He had conducted no dives in the prior 24 hours. Work during the dive was light to moderate. His risk of developing DCS would appear, therefore, to be based on diving to the edge of the no-stop limits and his age.

Symptoms. This patient's symptoms presented within a few minutes of surfacing from the above dive. Francis et al[15] argued that CNS DCS, particularly cerebral DCS, can present within 10 minutes following a dive. This is consistent with our experience in treating diving cases around the United Kingdom.

The symptoms described — dizziness, nausea, vomiting, loss of hearing, and difficulty with balance — can be ascribed to either DCS with inner ear manifestations or to inner ear barotrauma. The additional symptoms — slurring of speech and a general feeling of unwellness — would tend to argue for DCS.

The presence of a round window rupture and diagnosis of inner ear barotrauma was proven at operation. Inner ear barotrauma may occur in the

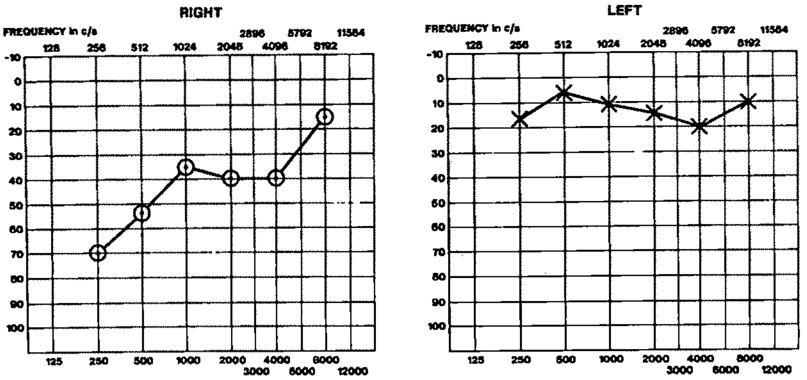

Fig 2. Follow-up audiogram completed following second recompression treatment on July 4, 1988.

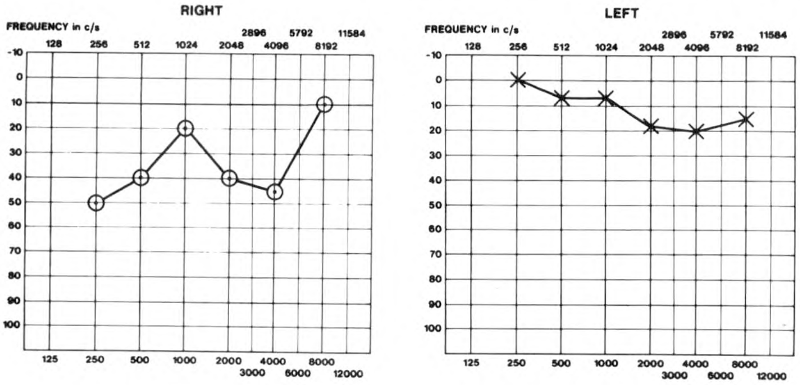

Fig 3. Follow-up audiogram completed on Aug 5, 1988, 1 month after surgical correction of round window fistula.

absence of overt difficulty with middle ear pressure equalization during a dive, and physical signs of middle ear barotrauma may not be present.[6] This man was not aware of any symptoms during the dive, but this is not an uncommon history. It should be noted that spontaneous resolution or improvement of symptoms caused by inner ear barotrauma may occur, but in this case, symptoms had been persistent over several hours. The coincident improvement with recompression to 9 m would be unlikely, as experience has shown recompression to have no positive effect on inner ear barotrauma.[12]

The evidence for DCS lies in several areas. Inner ear DCS following air diving is not commonly seen without some other evidence of CNS involvement. When it is an isolated finding it is more commonly due to a deep dive using mixed gas or saturation techniques.[9,11] The initial findings of slurred speech and a general feeling of unwellness led us to a trial of recompression. The resolution of the slurred speech during transit on oxygen, the improvement during recompression in Romberg's sign, the partial recovery of hearing within a few minutes at 9 m, and the continued recovery through a full 18-m treatment and second follow-up treatment argue strongly for the diagnosis of inner ear DCS.

Additional studies support this diagnosis. Auditory and visual evoked brain stem responses were normal, but the ^{99m}Tc-hexamethylpropyleneamine oxime brain scan revealed two areas of reduced cortical perfusion consistent with CNS disease. Ongoing research indicates that all cases of DCS with neurologic involvement display cortical lesions corresponding to symptoms and signs.[16,17] In this case, there was a significant area of reduced perfusion involving the auditory cortex on the right side.

Central lesions of the auditory cortex are not well understood. Clinically, unilateral lesions are difficult to recognize, usually producing subtle changes detected by alterations in performance on extensive, complex speech testing. A shift in the air conduction thresholds would not normally be expected on the basis of a temporal lobe disorder. Vestibular representation in the cerebral cortex is poorly defined in comparison to other sensory modalities, but cortical responses following stimulation of the vestibular nerve are primarily contralateral.

The minor hearing loss noted on the left side was not appreciated on initial examination, and it cannot be attributed to this accident with certainty. The need for rapid recompression precluded obtaining a pretreatment audiogram, and no previous audiograms were available. The presence of a central lesion in the auditory cortex is of interest, but its relation to any hearing loss would be speculative. More probably, it relates to the diffuse nature of CNS decompression sickness, contributing subtle changes to the more obvious symptoms and signs secondary to end organ involvement.

Pathology. Decompression sickness of the inner ear may be caused by a number of theoretic mechanisms. Most of these argue for an end organ involvement. Edmonds et al[11] gave a brief review of suspected mechanisms, which include 1) isobaric counterdiffusion with a gas-induced osmosis, endolymphatic hydrops, and damage to Reissner's membrane, 2) diffusion of gas across the round or oval window with endolymph saturation, 3) vascular emboli within the inner ear, 4) impaired perfusion

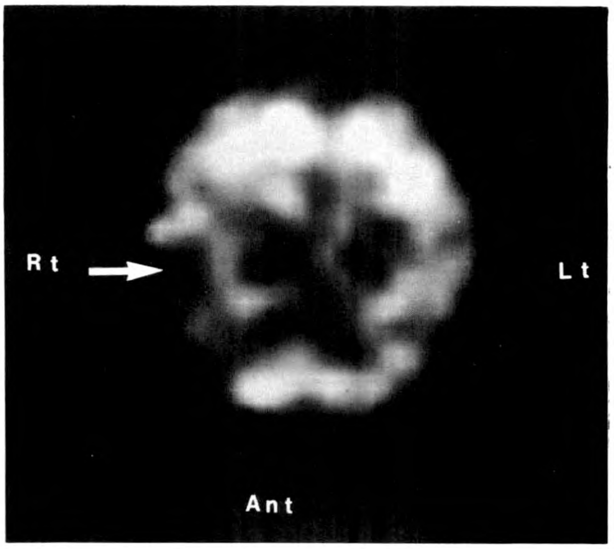

Fig 4. Transaxial view of isotope brain scan, showing ischemic lesion in right auditory region.

due to a localized collection of fluid such as the perilymph or endolymph, and 5) the presence of bubbles within the perilymph or endolymph creating an increased pressure in the labyrinth with resultant rupture of inner ear membranes.

More recently, Money et al[18] reviewed evidence suggesting a direct effect of expanding gas bubbles within the inner ear. Postmortem changes noted in human material matched experimentally induced changes previously seen in monkeys. The mechanism was postulated to be gas expansion leading to bleeding into or within the perilymphatic spaces of the cochlea. This may account, in part, for the hearing loss that can occur in DCS. Wilkes et al[19] have presented electron microscopic evidence of degenerative changes present in the organ of Corti in minipigs following stressful decompressions. The changes seen were felt to be the result of end organ involvement, with direct effects from rapid gas expansion leading to cellular degeneration. Hemorrhage was present, but appeared to play a much lesser role than formerly suspected (I. M. Calder, personal communication, 1989).

It has been demonstrated that there is a degree of cortical involvement in all cases of neurologic DCS. If a lesion of the auditory cortex is compounded by end organ involvement and then further by a round window fistula, it is easily postulated that hearing loss on the involved side would be significantly greater than any potential loss on the other side. The same argument applies for the vestibular component of this case. We suspect the hearing loss seen in this case was mediated through combined cortical and end organ disease. The entire picture was further complicated by the existence of a round window fistula.

When faced with the decision of whether symptoms are secondary to DCS or inner ear barotrauma, one should remember that a delay in the treatment of DCS is likely to negatively affect the outcome of the patient and that recompression should be effected as rapidly as possible. Recompression will not significantly affect the prognosis of inner ear barotrauma, as long as barotrauma is recognized in the differential diagnosis and treated appropriately if recompression is unsuccessful.

ACKNOWLEDGMENTS — We thank Surgeon Captain M. A. Macleod, RN, and the Nuclear Medicine and ENT departments at Haslar Royal Naval Hospital for their assistance in the management of this case.

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INHIBITION OF OSTEOCLAST RECRUITMENT AT A LOCAL SITE BY 1-HYDROXYETHYLIDENE-1,1-BISPHOSPHONATE (HEBP)

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We hypothesized that bisphosphonates, a class of antiosteolytic drugs that affect bone cells, may block localized bone modeling in the middle ear. Prior studies have shown that transmitted pressure in the middle ear leads to osteoclastic bone resorption. Catheters were surgically implanted into the middle ear cavity (bulla) of 31 Mongolian gerbils. The animals were then divided into two groups, one subset receiving a bisphosphonate, and the other receiving no drug. Positive air pressure was applied to one middle ear, and the other side served as a control. At the end of the experimental period, tissue specimens were obtained, and histomorphometric evaluation of the ventral bullae was performed. Significant differences in osteoclast surface, osteoclast number, and mean individual osteoclast profile area led us to conclude that administration of the bisphosphonate used at the dose studied inhibits localized recruitment and activation of osteoclasts.

KEY WORDS — bisphosphonates, gerbil, middle ear, osteoclast.

INTRODUCTION

Localized bone resorption and remodeling characterize fundamental pathologic processes that affect middle ear ossicles and cochlear and vestibular capsules in diseases such as otosclerosis and chronic otitis media.[1] The abnormal remodeling process is thought to be characterized by osteoclastic bone resorption succeeded by osteoblastic formation of primitive woven or lamellar bone.[2,3] Substances that inhibit the localized modeling and remodeling process may be useful in arresting or preventing these diseases.[3-6]

Bisphosphonates, compounds classified as antiosteolytic agents, are known to inhibit bone resorption[6-8] and may be useful in the amelioration of local bone resorptive processes in middle and inner ear disease. Although the mechanisms through which this inhibition occurs have yet to be determined, suppression of prostaglandin synthesis,[9,10] inhibition of osteoclastic mobility,[11,12] altered morphology,[13,14] decreased osteoclast recruitment,[15] and direct cellular effects[16-18] have been suggested. We proposed that a bisphosphonate could inhibit localized osteoclastic bone resorption in an in vivo model. In this study 1-hydroxyethylidene-1,1-bisphosphonate (HEBP) was given to gerbils in which localized bone resorption was induced in the pressurized bulla.[19] In this model, continuous positive middle ear pressure of 10 mm Hg applied to the bulla over 1 week results in a localized increase in the number of osteoclasts and the surface area covered by osteoclasts of the bulla wall without systemic effects.[20]

METHODS AND MATERIALS

Thirty-one 100-day-old male Mongolian gerbils, *Meriones unguiculatus*, averaging 65 g in weight (obtained from Tumblebrook Farms), were prepared by a single investigator. Each animal was anesthetized in a glass chamber containing methoxyflurane (Metofane). Fur from the dorsum of the head was removed, and the skin was sterilized with Betadine solution. A 1-cm transverse incision over the dorsum of the head was made through the skin and periosteum. After the skin was retracted, muscle and periosteum were reflected to expose the dorsal bullae bilaterally. A small diamond bur was used to make two 1.2-mm holes on the right posterolateral wall of the right bulla: one for incoming positive air pressure and one to monitor middle ear pressure to ensure a working system (Fig 1). A single 1.2-mm hole was made in the posterolateral wall of the bulla that was not pressurized and served as a control.

Catheters inserted into the bullae were prepared from 18-gauge stainless steel hypodermic needles. Each catheter was rendered free from burs and checked for patency before insertion into the bullae. A small screw was inserted into the skull posterior to the coronal suture to anchor the dental acrylic (Grip cement, R & R Dentsply, Maumee, Ohio), which was poured over the exposed areas of the calvarium, securing the catheters into the bulla. Once the cement hardened, polyethylene tubing (PE-160 Intramedic, Clay Adams, Parsippany, NY) was attached to the two steel catheters in the right bullae. The tube in the left (control) side was blocked with acrylic. One tube was attached to a pressure swivel and received positive air pressure delivered by an air pump; the other was plugged. Then a 3-mm-diameter stainless steel spring was positioned over the tubing to prevent the gerbil from chewing through the polyethylene. The pressure was main-

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From the Department of Otolaryngology, University of California, Davis, School of Medicine. Supported by a medical student fellowship grant from the Deafness Research Foundation and by National Institutes of Health grants R01 NS 21573 and R01 NS 21079. This study was performed in accordance with the PHS Policy on Humane Care and Use of Laboratory Animals, the NIH *Guide for the Care and Use of Laboratory Animals*, and the Animal Welfare Act (7 U.S.C. et seq.); the animal use protocol was approved by the Institutional Animal Care and Use Committee (IACUC) of the University of California, Davis.

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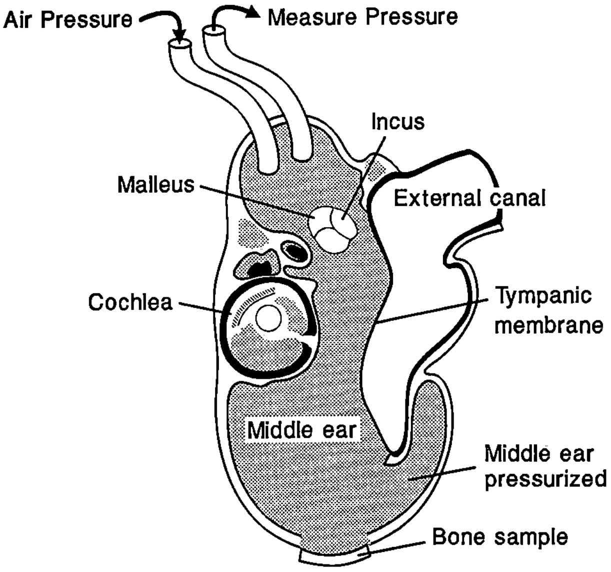


Fig 1. Diagram of coronal section through gerbil bulla showing location of implanted tubing. Stainless steel tubes are implanted into ventral bullae; air pressure is applied through one, and pressure is monitored through other. Shaded area is pressurized during experiment. Bone sample is taken, as shown, from dorsal area.

tained by a water column and monitored by a water manometer and an analog gauge to maintain a pressure of 10 mm Hg throughout the experimental period. The second tube, which was plugged, was used to check patency of the system at least twice daily. If a pressure tube was found to be blocked, the animal was excluded from the study. The animals were separated into two groups: gerbils in the experimental group received HEBP orally at 10 mg/kg daily in two divided doses, and those in the control group received no drug. Both groups were provided with adequate food and water and maintained on a 12-hour light-dark cycle schedule to avoid disruption of circadian rhythm patterns.

Histology. After the animals were killed painlessly, the ventral bulla was exposed to remove a 5 x 2-mm bone sample from the experimental (pressurized) and control (no additional pressure) sides. The tissue specimens were placed in Karnovsky's fixative (2% glutaraldehyde and 2% paraformaldehyde in 0.08 mol/L cacodylate buffer at pH 7.4) for 2 days, then decalcified in 0.1 mol/L EDTA in buffered 4% glutaraldehyde at pH 7.4 for 2 weeks. The specimens were dehydrated in graded solutions of acetone, embedded in Epon-araldite, and then sectioned to 0.5 μm. The sections were mounted on glass slides and then stained with toluidine blue and basic fuchsin. Slides were coded by a third party prior to histomorphometric analysis to prevent experimental bias. The codes were broken only after data collection and tabulation.

Histomorphometry. Those cells having a ruffled border juxtaposed to a bone surface and possessing at least two nuclei were identified as osteoclasts. Osteoclast surface (area of bone covered by osteoclasts divided by total bone area), osteoclast number (number of osteoclasts per millimeter of bone length), and individual osteoclast profile area in square microns were measured by use of a computerized histomorphometry analysis system (VIAS, Ted Pella) and an Olympus BH microscope.

TABLE 1. PERCENTAGE OF SURFACE OCCUPIED BY OSTEOCLASTS (MEAN ± SD)

	HEBP	*No HEBP*
Pressure	9.06% ±4.94%	18.19% ±10.25%
No pressure	5.84% ±5.90%	5.05% ± 4.19%

Statistics. Histomorphometric data were compared with Student's *t* tests for matched pairs when experimental bullae were compared to the contralateral control bullae, and Student's *t* tests for independent groups were used when comparisons were made between drug-treated animals and untreated control animals.

RESULTS

For ease of interpretation, the data will be discussed as follows: 1) comparison of the 17 experimental animals (those receiving HEBP) to the 14 control animals (no drug) that received positive air pressure (n = 31) and 2) comparison of the pressurized and nonpressurized sides in the HEBP-treated animals (n = 17).

HEBP Versus Control. In the bullae that were pressurized, we compared the HEBP-treated animals to a control group receiving no drug. The osteoclast surface area was significantly decreased (9.06% ±4.94%) when compared to that in untreated control animals (18.19% ±10.25%) (p = .002) (Table 1). The osteoclast number (number of osteoclasts per millimeter of bone length) was significantly decreased in the HEBP group (1.84 ± 1.31) when compared with the untreated control group (4.33 ± 2.54) (p = .001) (Table 2 and Fig 2).

Pressurized Versus Control. In the HEBP-treated animals we compared the pressurized side to the nonpressurized side. The osteoclast surface on the pressurized side was significantly larger (9.06% ± 4.94%) than that of the nonpressurized control side (5.84% ±5.90%) (p = .033) (Table 1). The osteoclast number was increased in the pressurized side (1.84 ± 1.31) compared to the control side (1.18 ± 0.61) (p = .019). The osteoclast profile area was not significantly changed in the HEBP-treated group (351.0 ± 21.6) when compared with the control group (389.8 ± 63.8) (p = .59).

TABLE 2. NUMBER OF OSTEOCLASTS PER MILLIMETER (MEAN ± SD)

	HEBP	*No HEBP*
Pressure	1.84 ± 1.31	4.33 ± 2.54
No pressure	1.18 ± 0.61	1.34 ± 0.66

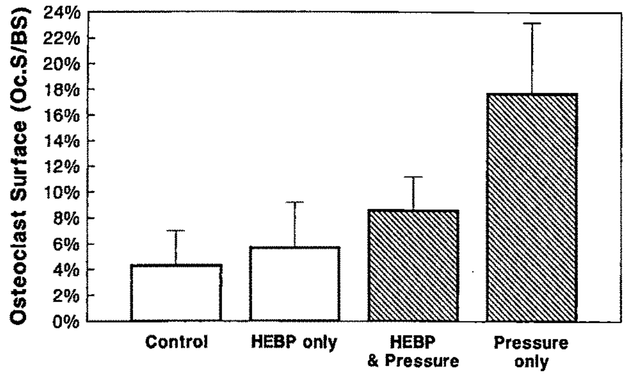


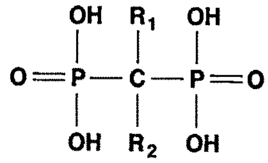
Fig 2. HEBP inhibits osteoclast activity in pressurized bulla when compared with pressurized, untreated animal (shaded bars). There are no significant differences when control, HEBP-treated-only, and HEBP-treated pressurized bullae are compared. Bars — plus or minus 1 SD, Oc.S/BS — ratio of osteoclast surface to bone surface.

DISCUSSION

The results indicate that HEBP inhibited pressure-induced osteoclastic bone resorption in the bullae of Mongolian gerbils. These findings support our original hypothesis that HEBP would block *localized* bone resorption in vivo. Previous studies have shown that bisphosphonates inhibit *systemically* induced bone loss.[21-23] In this study we have demonstrated that a bisphosphonate suppressed localized bone loss.

The mechanism by which inhibition occurs has not been established, although several have been proposed. One theory is based on evidence showing that synthesis of prostaglandins by bone cells is suppressed by bisphosphonates.[9] This action may be important, since prostaglandins and other arachidonic acid derivatives have been implicated in bone resorptive processes.[10,24,25]

Bisphosphonates bind to hydroxylapatite crystals in the bone matrix via direct nonhydrolyzable chemical bonds. This bonding can suppress mineralization and possibly inhibit bone resorption.[6-8] Osteoclasts may be affected indirectly following engulfment of bisphosphonate-bound matrix during the resorptive process.[8,16,26] Once entrapped, resultant relatively high concentrations could then alter osteoclast morphology [13] and metabolic functions.[9,16,18,27-29] Additionally, bisphosphonates might be released from the matrix locally with subsequent interference of processes through which mononuclear precursor cells differentiate into osteoclasts, resulting in recruitment suppression.[3,6,11,15] The altered osteoclast morphology and recruitment described by the researchers who offer these hypotheses are consistent with our findings from this in vivo model. Bone samples from the pressurized bullae of those gerbils receiving HEBP at 10 mg/kg per day had significantly fewer osteoclasts per millimeter and less osteoclast surface area than those of the control animals receiving no drug.



Bisphosphonate

Fig 3. General chemical structure of bisphosphonates. Substitutions at R1 and R2 groups change characteristics of compound.

Bisphosphonates may also inhibit osteoclastic migration, a process that promotes resorption as the osteoclast moves along the bone surface. In a study by Stevenson and Stevenson,[11] macrophages were chosen for their similarities to osteoclasts. They were found to have decreased motility when exposed to six different bisphosphonates. Bisphosphonate compounds differ from one another through modification of substituent R1 and R2 groups in the general formula of geminal bisphosphonates (Fig 3). The various structures enable differing degrees of activity with regard to physiochemical and biochemical processes and effects on mineralization and bone resorption.[11,19,27,28] Properties idiosyncratic to HEBP as compared with other bisphosphonates include inhibition of mineral formation in vitro and inhibition of bone resorption in vivo.[30]

Editronate disodium (HEBP) is presently used clinically in the treatment of Paget's disease,[31-33] and as a marker for diagnostic purposes in nuclear medicine.[34] Paget's disease is a metabolic skeletal disease that occurs as a result of an active bone resorptive process followed by appositional formation of primitive woven or structurally abnormal lamellar bone.[35] Although it primarily affects the axial skeleton, skull and temporal bone involvement can occur.[36] Narrowing of the internal auditory canal, destruction of the cochlear and vestibular capsules, and fibrous or osseous fusion of ossicles with hearing loss and/or tinnitus and vertigo can result from pagetoid changes to the temporal bone.[36-38] In clinical use, HEBP has had minimal side effects, while subjective symptoms of bone pain and elevated serum alkaline phosphatase and urinary hydroxyproline levels are improved in active Paget's disease.

Paget's disease can produce changes in bone that are similar to those observed in otosclerosis, in that both processes involve pathologic bone resorption and formation.[37-40] We propose that bisphosphonates could alter the course of otosclerosis and possibly prevent the hearing loss that occurs as the disease progresses.[36] Evidence from our study that demonstrates the effectiveness of HEBP in inhibition of bone resorption at a local in vivo site supports our proposition that HEBP could also inhibit pathologic bone resorption and formation in otosclerosis. The results of our animal study suggest that a clinical trial of HEBP for otosclerosis seems justified.

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Ann Otol Rhinol Laryngol 99:1990

EXERCISE IN PALEO-OTOLARYNGOLOGY: HEAD AND NECK EXAMINATION OF TWO EGYPTIAN MUMMIES

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Two Ptolemaic period mummies underwent head and neck examination including high-resolution tomography and endoscopic rhinoscopy and cranioscopy. The anatomy demonstrated characteristic laryngeal calcification and sexual dimorphism. Pathologic findings consisted of severe dental disease and possible chronic ear disease. Postmortem changes revealed the entrance of the embalmers into the cranial cavity, but raised interesting speculation regarding the method of brain removal.

KEY WORDS — ancient sinusotomy, embalming, mummy.

INTRODUCTION

Long before the Ptolemaic period (circa 300 BC), Egyptian mummification had evolved into a complex process whereby the body was first washed, eviscerated, salted, and desiccated. Then body cavities were packed with resins and linens, surfaces were covered with unguents and sometimes paint or gilding, and finally the body was thoroughly wrapped in as many as several hundred yards of linen. The most elaborate purification and embalming procedures are reported to have taken 70 days.[1] Ancient Egyptian religion dictated that the spirit of the deceased — if found worthy by Osiris, God of the Underworld, and other divine judges — was free for eternity to enjoy worldly pleasures in the netherworld. Maintenance of identity, safety from the dangers of the afterlife, and the quality of life after death were believed to depend on a well-preserved body entombed with all of the necessities of life on earth. These included toilet items and cosmetics, food, clothing, furniture, and servants (in the form of *shwapti* statuettes). The welfare of the spirit also necessitated that those visceral organs to which important functions were attributed (lungs, stomach, liver, bowel) be individually cleansed, desiccated, and wrapped and returned to the body or placed in four Canopic jars.[2] The heart, believed to control the mind and emotions, was thought to contain a record of its owner's good and evil deeds and was believed to be weighed against a feather in order to gain entrance to the netherworld. Because of its importance, it was left within the body.

Egyptian medicine, for its time, was fairly advanced. Notable Greek physicians benefited considerably from the medical institutions and library at Alexandria. Most medical literature reveals, however, a heavy influence of magic, aided by incantations, unguents, plasters, and nostrums to counter the external influences believed to cause disease states. A notable exception is the Smith Papyrus, a portion of a Middle Kingdom copy of an Old Kingdom treatise on the diagnosis and management of injuries to the head and neck.[3] Possibly written by Imhotep, a Third Dynasty physician, architect, and sage, this astonishing communication is the earliest known example of the use of the scientific method and an objective record of anatomic and therapeutic observations. In it are described such things as the pulsations of the living dura and the convolutions of the sulci and gyri of the cortex. Also found in it is the concept of lost motor control from contralateral head injury. Despite these early observations, no specific function was generally attributed to the brain, and during mummification it was removed from the body but not preserved.

While it is known that the brain was usually removed through the nose and cribriform plate without further craniotomy, exactly how this was accomplished is unclear. Contemporary descriptions suggest both the use of a small curved instrument and the employment of a caustic liquid used to liquefy the brain, which then could be simply poured out.[4] One can speculate that brain tissue might liquefy quickly without much help in the North African heat. A study of the head and neck region was undertaken as part of a multidisciplinary examination of two Ptolemaic period mummies housed in the Egyptology collection of Memphis State University, Memphis, Tennessee. This was facilitated by the previous removal of linen wrapping from the head and neck of each specimen. Attempts were made to determine the general state of health of the individuals during life as well as to ascertain any possible clues to their cause of death. Specifically in

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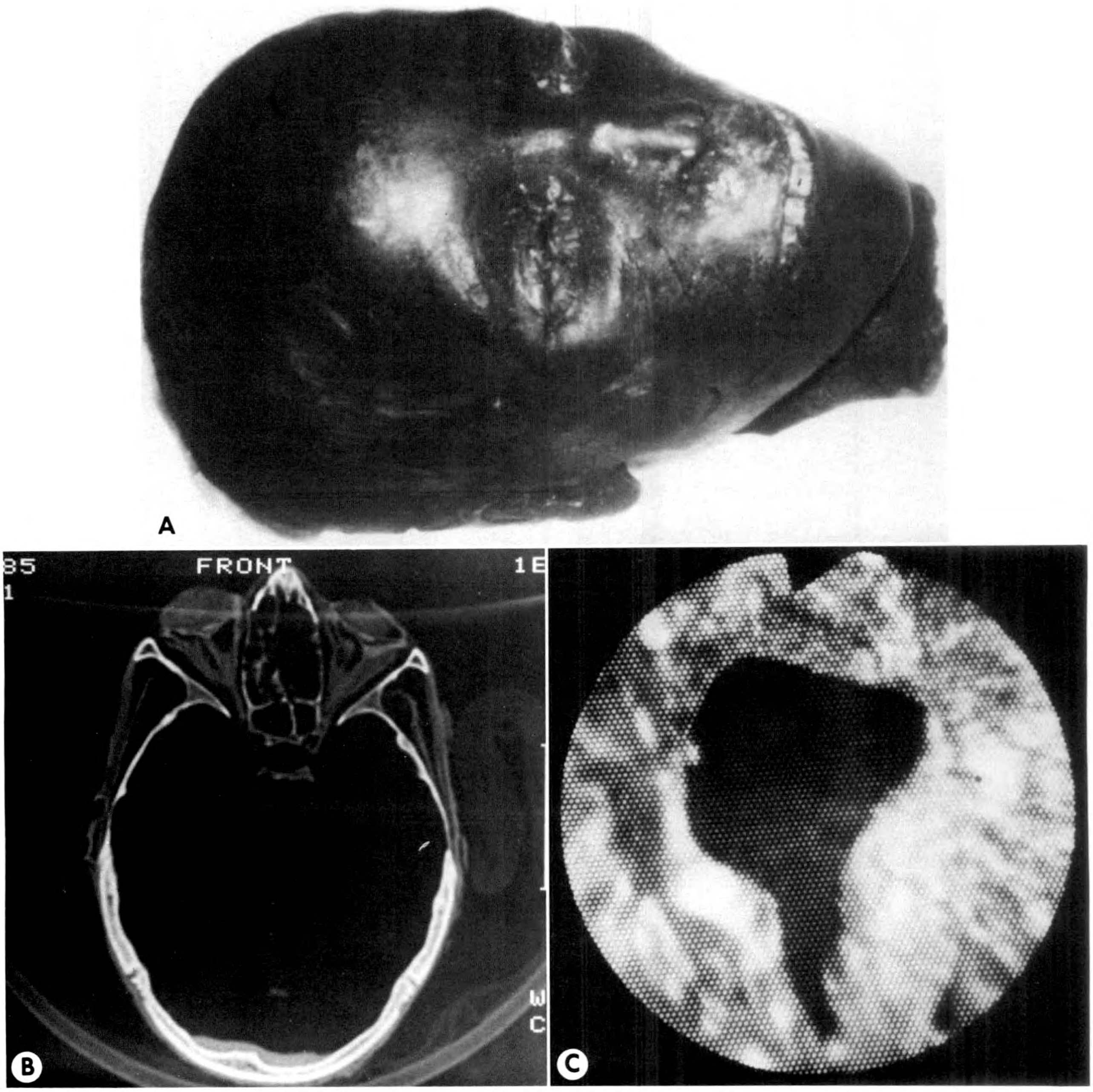

Fig 1. (Se-Ankh) A) Well-preserved head of Ptolemaic period Egyptian mummy. B) Computed tomogram of head at level of ethmoid sinuses. Note postmortem removal of left ethmoid system and displacement of septum toward opposite side. Globes are compressed behind linen packs within orbits. There is absence of intracranial resin or packing. C) View through flexible nasopharyngoscope showing hole in fovea ethmoidalis and cribriform plate on left side.

the head and neck region, attention was directed to the method of brain removal and other mummification practices as they related to this anatomic arena. A systematic search for evidence of otolaryngologic disease was also conducted.

SPECIMEN HISTORIES

Se-Ankh ("brought to life") is an isolated mummified head contemporaneously named by the Memphis State Director of Egyptology, since it arrived with no record of name or place of origin. It is exceptionally well preserved, as can be seen by casual observation (Fig 1A). Se-Ankh left Egypt in the company of an American adventurer, Archibald Marvine, in the 1850s; thus, it is one of the earliest human artifacts from ancient Egypt to reach the New World. After generations of storage by family members, the head was loaned to the Memphis State collection.

The presence of a rosette applique on the right temple allows presumptive dating of the mummy to the Ptolemaic (Greek) period (304 to 330 BC).[2] This period is further suggested by evidence of gold gilding of the skin, which characterizes mummies of both the Macedonian (332 to 304 BC) and Ptolemaic eras. On the basis of skeletal measurements, dental maturity, and style of mummification, it is speculated that Se-Ankh was a woman, 30 to 40 years of age at her death, who was a member of the Egyptian nobility at a period of intense Hellenistic influence. Her diet included enough grain with admixed grit that her teeth were markedly worn. Her hair was close-cropped by razor cutting and undoubtedly was covered most of the time by wigs, a hygienic and social custom of the time. No cause of death could be determined.

Iret-Irew ("may the eye of God be against them") was purchased from a Detroit, Mich, pawnbroker and arrived in Memphis together with a decorated coffin, gilded mask, and pectoral. The mummy was completely wrapped except for the head and a foot. The burial style of the accessories dates Iret-Irew to the Ptolemaic period and suggests an origin in Akhmim province. Iret-Irew was male and in his sixth decade when he died. He was 157 cm (5 ft 2 in) in height, average for a man of that era, and enjoyed considerable wealth and social prestige, as evidenced by the manner in which his body was treated after death. He also is well preserved, although a portion of the left lateral part of the neck has been lost.

MATERIALS AND METHODS

Routine anterior-posterior and lateral radiographs were obtained, as well as an orthopantanogram on Se-Ankh, the only specimen of the two able to be positioned for this scan. The intracranial space, sinonasal tracts, and upper aerodigestive tract and neck of both mummies were studied by high-resolution computed tomography (CT) on a Siemens DR3 unit, with use of 4-mm cuts. The temporal bones were imaged with 2-mm cuts and a variety of high-resolution imaging processing algorithms.[5]

The sinonasal tracts and intracranial space of both mummies were visually investigated with flexible (Olympus ENF, P-2) and rigid (Storz) endoscopes via either the nose (Se-Ankh) or a cranial bur hole (Iret-Irew). A digital video camera was used for monitoring, and recordings were made on a videocassette recorder. Thirty-five–millimeter transparencies were taken of these spaces with an Olympus OM-2 camera on 400 ASA Ektachrome film.

FINDINGS

Temporal Bones. Even in a normal living subject, the soft tissue within most of the temporal bone is sufficiently thin to not be visualized by CT. In these preserved specimens, all soft tissue had been desiccated. Thus, the radiographic examination was one predominantly of the bony architecture with the exception of a possible pathologic process in one ear as discussed below. Because most findings in all four bones were similar, they will be discussed together, with individual bones discussed only as exceptions.

External Ears. The external auditory canals were of normal dimensions and air-containing in Iret-Irew. The canals of Se-Ankh were normal but filled with a moderately electron-dense material consistent with either cerumen or products of the embalming process. The auricles of Iret-Irew had been wrapped forward by the linen bandaging in a somewhat unlifelike position. What small amount of wrapping remained on the head did not appear to have been fashioned into a bolster expressly for this purpose (Fig 2A).

Middle Ears and Mastoids. The mastoid systems were all pneumatized with sharp bony trabeculae, arguing against significant childhood inflammatory disease. The tympanic space of each ear was of normal dimensions and the ossicles could be seen to be in the anatomic position and intact. The left attic of Iret-Irew contained a spherical mass adjacent to the bodies of the ossicles, obscuring their fine structure on that side (Fig 2B). No evidence of bone erosion could be identified. While this material was of the same radiodensity as the embalming resin layered out in other body spaces as described below, because of its nonlayered shape and location in an other-than-dependent site, chronic inflammation, cholesteatoma, or tumor could not be ruled out.

Inner Ear and Otic Capsule. Both cochlea and labyrinth of all four bones were of normal morphology. The internal auditory canals were symmetric and of normal diameter. The cochlear aqueducts were surprisingly prominent in all four ears, but appeared to be of normal dimensions. The vestibular aqueduct was less easily visualized, but its opercular opening was seen to be normal in all bones. The right otic capsule of Se-Ankh contained a widened pterygomastoid fissure. This developmentally important vascular channel contains the subarcuate artery and is occasionally seen in contemporary adults. It could not be identified in the other three ears. Both Se-Ankh and Iret-Irew had dominant right jugular bulbs deeply imprinting the undersurface of the petrous apex. Their left systems were barely discernible.

Sinonasal System. Neither specimen had frontal sinuses of any size, the right side of Se-Ankh being completely nonpneumatized. The right ethmoid system of Se-Ankh was normal, containing seven or eight individual cells, but the left had been turned into a single cavity (presumably postmortem) with displacement of the septum severely to the right (Fig 1B). The nasal passages and other sinuses were clear and contained air. Iret-Irew showed removal of air cells of both ethmoid systems with left septal displacement and herniation of orbital contents, including linen packing, through violated laminae

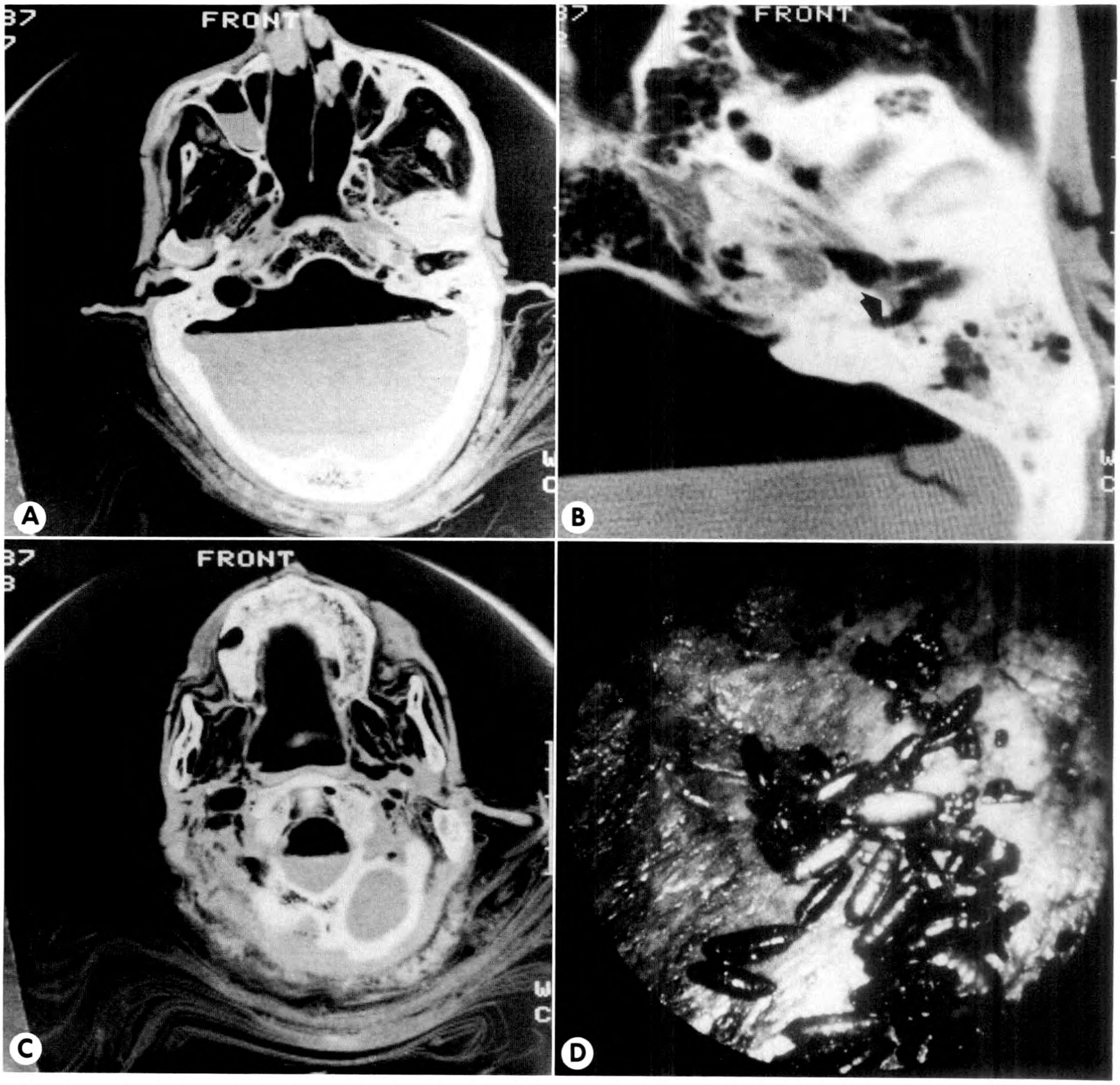

Fig 2. (Iret-Irew) A) Computed tomogram of head at level of jugular bulbs demonstrating asymmetry of bulbs, layered resin in posterior fossa, anterior bending of pinnae, resin in right maxillary sinus, and three round plugs occluding nasal passages. B) Computed tomogram of left temporal bone demonstrating soft tissue mass (arrow) between promontory and malleus at level of sinus tympani. Note modestly pneumatized mastoid, basal turn of cochlea, and posterior semicircular canal. C) Computed tomogram at level of maxillary alveolus. Note distinct periapical abscess cavity on right. There is resin in foramen magnum, and layers of linen wrapping can be seen behind occiput. D) View through rigid endoscope showing varieties of insect larvae within sealed cranial vault.

papyraceae into the nose. Also evident were globular nasal plugs, two on the left and one on the right, that radiographically were seen to contain bits of radiopaque material. The cranial vault, left frontal sinus, and right maxillary sinus of Iret-Irew had dependent air fluid levels representing solidified products of embalming. The sphenoid sinuses were nonpneumatized in this specimen.

Dental Apparatus. An extensive description of Se-Ankh's teeth and jaws has already been published.[6] Essentially, there was an absence of many molars, especially on the left, with a few retained roots and evidence of caries. There was marked occlusive wear, especially on the right, thought to be due to grit and sand admixed with the grain products making up a substantial portion of the diet. Other findings were a periapical dental cyst, generalized periodontal disease, and evidence of left mandibular osteomyelitis.

Review of the CT scan of Iret-Irew's teeth and jaws demonstrates few missing teeth but multiple caries and apical abscesses with various degrees of alveolar resorption (Fig 2C). As with Se-Ankh, the mandibular condyles, seen on temporal bone reconstruction, were smooth and regular.

Upper Airway. The larynx and trachea were not well differentiated in either specimen, in part because of some anterior-posterior compression due either to tight wrapping following embalming, or the subsequent years of handling during their long sojourn to Memphis. The thyroid cartilage was easily discernible and was noted to form an obtuse angle anteriorly in Se-Ankh and an acute one in Iret-Irew, consistent with the sexual dimorphism characteristic of this structure. Both thyroid cartilages also contained differential areas of ossification, also a sex-linked variable, that were useful in determining the ages of the individuals at the time of death. The hyoid bone, cricoid cartilage, and epiglottis could also be seen in the CT sections along with some of their soft tissue attachments, but true and false vocal folds, arytenoids, and cricoarytenoid and cricothyroid joints were not definable. The styloid process of Iret-Irew was prominent bilaterally, but did not reach the hyoid bone. The cervical tracheal rings and lumen were identified as collapsed in both specimens. The trachea assumed its normal configuration in Iret-Irew at the thoracic inlet.

Endoscopic Intracranial Examination. A fiberoptic nasopharyngoscope was passed through the left nasal passage of Se-Ankh. The mucosa was noted to be desiccated, with an investment of resinous material on its surface. The scope could not be passed into the nasopharynx without risking damage to the external nose by levering against the ala. A 1.0 x 0.6-cm hole through the cribriform plate and fovea ethmoidalis was easily visualized and seen to have clean, sharp margins (Fig 1C). Advancing the scope through the hole afforded a view of the anterior cranial fossa and the attachment of the falx cerebri, which was absent. Likewise, visualization of the petrous pyramids showed no evidence of even remnants of the tentorium. The etchings of the branches of the middle meningeal artery on the inner surface of the squamosa of the temporal bone were crisp and no scratches or other man-made evidence of postmortem manipulations could be seen. At the bottom of the posterior cranial fossa, material consistent with the ampullated end of the spinal cord was seen in the spinal canal through the foramen magnum. In several regions of the intracranial space but primarily on the petrous apices, pale cylindric masses measuring approximately 0.2 x 0.5 cm were encountered. These appeared to represent at least two different species of insect larvae.

In the case of Iret-Irew, the previously noted nasal plugs precluded an endoscopic examination by the transnasal route. Consequently, a 4.0-mm bur hole was made in the right temporal region in a site of artifactual soft tissue loss. The nasoethmoid region was examined in a retrograde fashion, the inner aspects of the nasal plugs being evident on either side of a deviated nasal septum skeletonized by the bilateral postmortem ethmoidectomies. As in the case of Se-Ankh, no evidence of remaining dura could be found, vascular markings were sharp, and no instrumental scratch marks were seen. The surface of the bone had a thin coat of a brownish orange crystalline material applied to it that glistened in the bright endoscopic light, and the dependent portion of the posterior cranial fossa contained a layered blackish solid — presumably a hardened liquid instilled at the time of embalming (Fig 2A). Insect larvae were everywhere adherent to the inner surface of the skull — some pale, some dark — and of at least three different varieties (Fig 2D).

DISCUSSION

The opportunity to study these two specimens allowed a comparison of contemporary head and neck anatomy with a sample from 2,000 years ago of a genetic pool believed to be most closely related to the present Coptic Christians of North Africa.[7] On a broader scale, it allowed insight into the lifestyle and otolaryngologic health of one social class of ancient Egyptians as well as an examination of the funeral rites of their religion as they related to the head and neck. Modern methodology supplemented the pioneering multidisciplinary approach taken at the University of Manchester a decade ago.[8]

Anatomic study, not surprisingly, revealed head and neck parameters falling within the range of modern normal variations. Both specimens appeared to be petite and fine-featured, with relatively large nasal bones and absent nasal spines; the latter finding was evident in lateral radiographs of other mummies.[9,10] Neither had particularly well-developed paranasal sinuses. The frontals of Se-Ankh and the sphenoids of Iret-Irew were essentially nonpneumatized; in modern specimens this finding is present roughly 5% of the time.[11] The mastoids, as well, were only modestly pneumatized, without any features of acquired contraction or "sclerosis." The mastoids of another Egyptian mummy temporal bone studied histologically were demonstrated to be well pneumatized by today's standards.[12] The bony anatomy of all four ears would be considered radiographically "normal." The prominence of the petromastoid tract seen in the right ear of Se-Ankh might have been unilateral, or perhaps it was simply not represented in the particular 2-mm cut of the opposite side. Such a tract is also occasionally seen in modern temporal bones and may be associated with an enlarged subarcuate artery.[13] It was not described as being present in the temporal bone examined histologically as noted above.[12] Evidence of a dominant right jugular venous drainage system in each skull is also consistent with current norms. The general morphology and ossification patterns of the thyroid cartilages could be characterized and were entirely consistent with the suspected age and sex of the two individuals studied.

Pathologic findings were suspected to a lesser or greater degree radiographically, but in no instance proven by histologic techniques in our specimens. There appears little doubt as to the nature of the dental crown wear, caries, and apical abscesses of these two individuals. The rarefaction of the right mandible of Se-Ankh appears entirely consistent with osteomyelitis. On the other hand, the spherical soft tissue mass in the left tympanic cavity of Iret-Irew, especially with the absence of any evidence of bone erosion, only raises the possibility of chronic otitis or a glomus tympanicum tumor.

Findings attributable to the processes of embalming and preparation for entombment are similar to those described in previous reports of radiographic study of Egyptian mummies from a variety of dynasties.[8,9,12,14,15] Removal of the brain through an anterior cranial fossa approach via the sinonasal tract without recourse to other craniotomies appears to have been a standard technique for many centuries. Most of the details of the method of removal have been lost, probably in part as a result of the magical elements of mummification and the guildlike exclusivity of the priest/embalmers who accomplished it. There is one account of curved instruments' being used to remove brain tissue, but this seems an unlikely explanation for the absence of dura, which is difficult to strip from the base of the skull even with full exposure.[4] The inner surface of the calvarium and the base of the skull showed no evidence of scratches or soft tissue remnants as might be left behind by scraping instruments. A corrosive fluid has also been speculated to facilitate pouring the brain out of the calvarium.[4] The enzymatic activity of papain may have been available to Egyptians in the form of papaya, and weak acids (vinegar) from end-stage fermentation were certainly being produced. Still unexplained by this hypothesis is the absence of dura. Furthermore, the etching of the middle meningeal artery of the inside table of the temporal squamosa was sharp and showed no evidence of blunting as might have been caused by dissolution or softening by an acid solution. Removal of the brain was by no means universal and examples of remaining brain tissue exist from several periods of Egyptian antiquity.[4,16]

The orbits of both specimens were filled with linen strips, collapsing the globe and interocular muscles posteriorly and holding out the form and position of the lids. Embalming practices varied with regard to orbital contents, which were allowed to collapse in the early dynasties and were sometimes replaced with wax in later dynasties.[4,15,17] The plugs in the nostrils of Iret-Irew are presumed to serve the same function for the cartilaginous nasal tip, although the appearance of Se-Ankh would argue that it was unnecessary. Other anatomic areas occasionally received subcutaneous packing of linen, wax, or sand, especially in more recent specimens.[15,17,18] Solidified resin layering out in dependent areas of the cranial and visceral cavities is believed to be particularly characteristic of mummies of the Ptolemaic period.[19] There was no apparent reason for the second plug in the left nostril of Iret-Irew. The protuberant position of the auricles caused by the linen wrapping of Iret-Irew was presumably intentional and has been described in at least one other Egyptian mummy of the Ptolemaic period.[12]

When the insect larvae were found during the endoscopy of Se-Ankh, it was assumed that these were contemporary Memphis (Tennessee) insects acquired by the mummy during its storage in an attic. The finding of similar larvae in the cranial cavity of Iret-Irew, whose nasal craniotomy had been sealed 2,300 years previously by plugs, made it likely that all larvae were as ancient as the human remains in which they resided. One beetle larva of a species often found in carrion has been described in the resin in the external auditory canal of an Egyptian mummy.[12] Examination of insect larvae present in the tissues of one mummy in the Manchester University collection demonstrated many puparia of *Piophila*, a dipteran fly and a pest in stored meat. Other mummies were found to contain puparia of *Chrysomyia*, another dipteran fly, and a few puparia of the common house fly, *Musca*. The authors speculated these insects were introduced to the bodies postmortem, but pre-embalming, although some evidence exists that some may have been introduced following later rehydration due to flooding.[8] One would expect embalmed dura to be at least as permanent as nasal mucosa. It is difficult to visualize how dura, which is firmly attached to the cranium, could be so completely stripped, especially from the posterior fossa, by an instrument introduced through the nose. Several other mummies of later dynasties are described as having an intact falx or dural remnants identified on CT scans.[15,19] Perhaps insects aided the liquefaction or removal of the brain or entered the cranium following its removal and devoured the dura early in the embalming process, only to fall victim to later stages of the process and became enbalmed themselves. The removal of the dura then might not ever have been the intent of the embalmers.

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INTERPRETING THE SOUNDS OF SWALLOWING: FLUID FLOW THROUGH THE CRICOPHARYNGEUS

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The sounds of swallowing in normal subjects were recorded by means of a miniature accelerometer on the throat, simultaneously with videofluoroscopy of a modified barium swallow. Consistent correspondence was found between a rapid change in the acoustic spectrum of the accelerometer signal (the appearance of a region of energy prominence above 1,000 Hz) and bolus flow through the cricopharyngeus.

KEY WORDS — acoustics, cricopharyngeus, swallowing, videofluoroscopy.

The sounds of swallowing can be heard by cervical auscultation. On the basis of clinical experience it seems that the sound of a normal swallow may be distinguished from the sound of a dysphagic swallow. In some dysphagic patients, especially those with pharyngeal involvement, the sound is less sharp, or even bubbly if aspiration has occurred.

The standard clinical examination of swallowing employs videofluoroscopy, with its attendant radiation exposure. Although in some settings other methods are also used for swallowing research and clinical assessment (ultrasonic scanning, scintigraphy, manometry), all require costly equipment and sophistication for interpretation. Auditory or automated acoustic analysis of swallow sounds could become a useful noninvasive aid in alerting a clinician to the presence of swallowing dysfunction, or tracking its course in dysphagia treatment.

The usefulness of acoustic analysis in swallowing is presently restricted by lack of validating research on the physiologic source of the sounds heard and on their variation with different bolus properties and in disordered deglutition.[1] Documentation of physiologic correlates in the form of quantifiable data is an important first step.

The early literature describing acoustic phenomena associated with deglutition most often reported using the sound recorded from the throat to mark the occurrence of swallowing.[2-6] Descriptive reports of throat microphone signal analysis agreed that the acoustic signature of a normal swallow consists mainly of two distinct temporal components, sounding like a double "click."[2,3,7] Although there is considerable individual variability, a first 50-millisecond component is followed by a longer 150- to 200-millisecond burst.[7] In a wet swallow a third, brief, low-amplitude component may be heard 300 to 400 milliseconds later.

Spectral analysis of swallowing signals has revealed both aperiodic and periodic components[1] (also J. S. Heinz et al, unpublished observations, 1986), although the aperiodic noise bursts constitute the major and most consistent characteristic. The concentration of acoustic energy is below 3,000 Hz in swallow signals recorded both from the throat and from the external ear canal.[1,8] A spectral change within the signal for a wet swallow has been noted, consisting of an upward shift in energy concentration from 400 or 600 Hz at the beginning to a peak near 1,000 Hz at the end of the swallow.[7] That report did not specify the number of subjects or swallows investigated, nor the volume of the bolus. Spectrographic displays of swallow sounds are distinct from those of cough, respiration, and vocalization.[3]

A limitation of previous acoustic studies of swallowing is lack of validation for the physiologic correlate of the sounds. The present paper reports an analysis of swallow signals recorded simultaneously with videofluoroscopic tests of swallowing function in normal adults. The emphasis is on acoustic correlates of fluid flow through the cricopharyngeus.

METHOD

Ten normal subjects between the ages of 40 and 61 participated. They were serving as normal healthy controls in a study of deglutition in head and neck cancer patients, and were undergoing videofluoroscopic tests of swallowing function. Analysis was based on a total of 30 swallows from the 10 subjects.

Swallowing signals were recorded from the throat with a miniature accelerometer (Vibrometer 501M601) affixed to the skin with double-sided tape. An accelerometer transduces surface vibration and provides a high-quality signal similar to that from a contact microphone. The location of the accelerometer was about 2 cm below the angle of the mandible, over the lateral portion of the thyrohyoid

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membrane, with the larynx at rest. None of these normal subjects was significantly overweight or underweight, so that the potential problem of obtaining a good accelerometer recording from the throat of a subject with excess neck fat was not encountered.

Videofluoroscopic tests of modified barium swallows (cookie studies) were done for each subject. Both lateral and anteroposterior views were included for swallows of 10 mL of liquid barium suspension (40% weight per weight). The accelerometer signal was recorded on an audio channel of the video recorder. Video frames were identified by a numeric video timer signal accurate to centiseconds. Synchronization of the audio and video channels was accomplished by delivering a tone burst to the audio channel as the video timer was halted at the same number for three frames.[9] This was accomplished by manually pressing a button as the instruction to swallow was given, or shortly after completion of the swallow. In this way exact temporal alignment of the two channels could be determined during subsequent analysis.

Acoustic analysis of the accelerometer signals made use of Micro Speech Lab software available for an IBM-PC. The accelerometer signals were high-pass filtered at 200 Hz and digitized at 6,000 Hz (permitting spectral analysis from 0 to 3,000 Hz). The accelerometer signal was displayed on the computer monitor, and the temporal location of the synchronizing tone burst was determined. Then a 1-second interval containing the swallow was edited out for analysis. This signal could be played back by the computer for listening. An 85-millisecond time window was moved through the 1-second waveform displayed on the monitor, and the windowed segment was played back until a portion of the signal was identified in which a rapid pitch change was heard. Prior work had determined that this signal characteristic, which tends to occur during the highest-amplitude portion of the swallow signal, is the most salient auditory aspect of the sound of swallowing.[1]

Once the location of the perceived pitch change (within the 85-millisecond time window) was identified, detailed spectral analysis was done within that time window by use of Fourier analysis. Fourier analysis is a mathematical method for computing the acoustic spectrum of a brief segment of an acoustic signal. The result of the computation is then displayed as an amplitude-by-frequency plot like that illustrated in Fig 1. Sequential 128–sampling-point fast-Fourier transform analyses were run, until a temporal location was identified at which the spectral concentration changed markedly. The spectrum was displayed and printed at that temporal location. Then the 128–sampling-point window was moved back 40 milliseconds earlier, and a second spectrum was computed. A spread of 40 milliseconds ensured that the two 128–sampling-point windows did not contain temporally overlapping signal components. These two spectra, 40 milliseconds apart, formed the basis of the calculations for spectral shift.

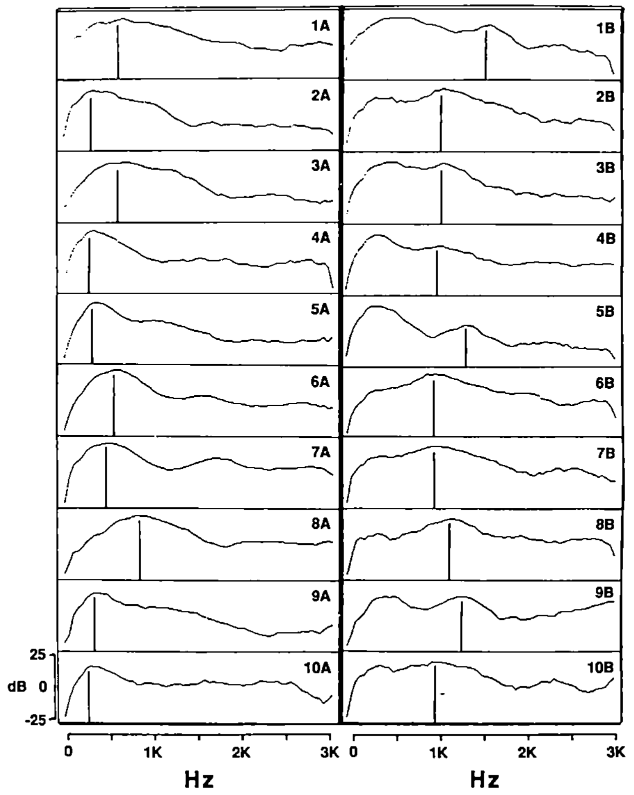

Fig 1. Examples of spectral shift between time points 40 milliseconds apart within accelerometer signal recorded during deglutition. One example from each subject is illustrated. Left column (A) represents earlier time point, with right column (B) showing spectra for first 21-millisecond time window demonstrating higher-frequency energy peak.

The simultaneously recorded videofluoroscopic data were then analyzed. The video frame corresponding to the acoustic spectral shift was identified. Location of the barium bolus was noted. The videotape was then scanned frame by frame until a frame was identified in which the leading edge of the barium bolus began to enter the cricopharyngeus. The results of the independent acoustic and videofluoroscopic analyses were compared to determine whether there was a correspondence between bolus flow into the upper esophageal sphincter and the time of the spectral shift.

RESULTS

Two spectra 40 milliseconds apart were computed for each of the 30 swallows. There was a marked and audible shift in spectrum between these two points. The earlier spectra had an energy peak in the low frequencies: an average center frequency of 556 Hz (Fig 1). The spectra 40 milliseconds later displayed a prominent region of energy centered at an average of 1,384 Hz, although this was not

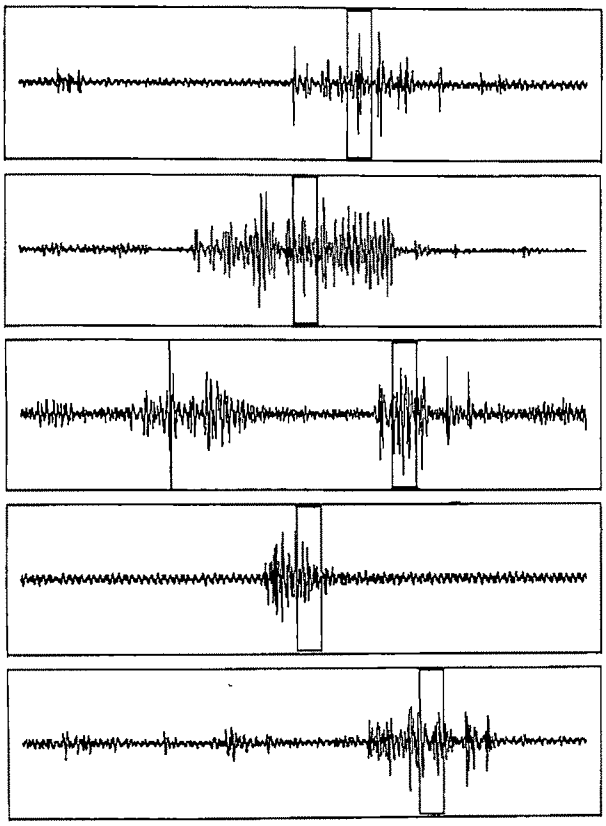

Fig 2. Time waveforms of accelerometer signal recordings from throat during swallowing. Window indicates point at which there was marked spectral shift, such as is illustrated in Fig 1.

necessarily the highest-amplitude portion of the spectrum. All swallows analyzed were qualitatively similar in this respect; the average difference in spectral peaks at these two temporal locations was 828 Hz (range, 328 to 1,922).

It should be noted that there was only one portion of each swallow signal having this characteristic spectral shift. Figure 2 illustrates the point in the time waveforms of several accelerometer signals at which such a spectral shift occurred. When there was more than one discrete aperiodic component in the swallow signal, the spectral shift occurred in the last high-amplitude segment. The amplitude peak of the swallow signal waveform did not invariably correspond with this spectral shift, nor did the overall duration of the aperiodic swallow signal correspond to the time it took the bolus to pass through the upper esophageal sphincter. These points are being emphasized, not as negative results, but to point out that extracting important information from the acoustic swallow signals requires analysis beyond simple visual inspection of the waveform.

There was a temporal correspondence between the point at which a region of energy prominence above 1,000 Hz appeared in the spectrum, and flow into or through the cricopharyngeus. The spectral shift occurred an average of 37 milliseconds after the video frame showing the bolus leading edge entering the cricopharyngeus. The Table gives the distribution of correspondence in terms of numbers of video frames. Since the video frame rate is 30/s, each frame encompassed 33 milliseconds, resulting in this margin of error in the comparisons. There was a correspondence within one video frame for 20 of the swallows. In the remaining swallows the spectral shift occurred after the bolus head had entered the cricopharyngeus, but not before the bolus had fully passed into the esophagus.

TEMPORAL DISCREPANCY BETWEEN ENTRY OF BOLUS INTO CRICOPHARYNGEUS AND POINT OF SPECTRAL SHIFT IN ACCELEROMETER SIGNAL

Video frames (33 ms each)	0	+1	+2	+3	+4	+5
Swallows	20	3	2	3	1	1

Positive number of video frames means spectral shift occurred after videofluoroscopic evidence of bolus flow.

DISCUSSION

There was a consistent correspondence found between a spectral shift in the accelerometer signal and bolus flow into and through the cricopharyngeus. It was not possible to identify the onset of bolus flow into the cricopharyngeus by the visual onset of the major noise burst in the sound of swallowing, nor did this event correspond regularly to the maximum-amplitude portion of the waveform.

In interpreting the source of the sounds of swallowing, the physical conditions in the lower pharynx should be recalled. Simultaneous manometry and videofluoroscopy during swallowing[10,11] has demonstrated that the bolus head enters the pharyngoesophageal segment almost simultaneously with a sharp increase in pressure that represents the pressure of the tongue base moving posteriorly (T-wave). Thus, the bolus is normally under pressure before moving through the cricopharyngeus. We propose that it is the increase in bolus velocity corresponding to the onset of *pressurized* flow into the esophagus that is generating the characteristic spectral shift in the swallowing signal. The mere fact of bolus entry into the esophagus, by gravity alone for example, would not be sufficient to generate such a sound. Likewise, the duration of the swallow signal (or particular components of it) should not be expected to necessarily correspond to visual locations of the bolus without concomitant force behind its movement. Further research on the physical conditions of bolus propulsion and flow characteristics through the cricopharyngeus is important for a full explanation of the generation of swallow sounds.

If the general explanation provided above is valid, this would predict that a swallow with weak bolus ejection by the tongue, or an unusually relaxed cricopharyngeus, would be accompanied by weak or even no spectral shifts in the swallowing sounds. Further, if cricopharyngeal stricture is present and the swallow must commence under undue pressure, as it may in laryngectomy patients,[11] swallowing sounds with deviant spectral patterns would be anticipated. These issues are currently under investigation.

Other features of swallow signals recorded from the throat may have consistent physiologic correlates to such activities as laryngeal elevation and the epiglottis's returning upright after completion of the swallow.[1] It has been suggested that a brief periodic component of the swallow signal may signal glottic closure during the swallow (Heinz et al, unpublished observations, 1986). There is a great deal of additional research needed to explore these possibilities.

The use of an accelerometer against the throat as a means of documenting the presence and temporal location of a swallow remains a useful tool. This research gives more confidence in using such a technique for a normal swallow. It is also possible to interpret the conditions present at the time of the pitch change characteristic of a normal swallow.

ACKNOWLEDGMENT — The authors thank Lewis Jones, MD, for his assistance in obtaining videofluoroscopic data.

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IMAGING CASE STUDY OF THE MONTH

MAGNETIC RESONANCE IMAGING TO DISTINGUISH TUMOR PERSISTENCE FROM DELAYED FIBROSIS IN CARCINOMA OF THE TONGUE AND FLOOR OF THE MOUTH

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CASE REPORT

A 44-year-old woman was first referred to UCLA in May 1984 for evaluation of swelling of the right lateral aspect of her tongue associated with decreased mobility of the tongue. She first noted this abnormality 8 months earlier. A biopsy at UCLA indicated reactive epithelial hyperplasia with no evidence of malignancy, and results of a computed tomography (CT) scan were interpreted as normal.

Three months after being seen at UCLA the patient noted the onset of a right-sided neck mass and returned to her own doctor. He repeated the tongue biopsy, which revealed a moderately differentiated squamous cell carcinoma. A repeat CT scan was also performed; it showed a 3-cm right jugulodigastric node, but did not reveal any abnormality within the tongue (Fig 1A). The patient was then referred back to UCLA, where a magnetic resonance imaging (MRI) examination was done with use of a 0.3T permanent magnet imaging system (Fonar B 3,000, Melville, NY). The images were acquired with a two-dimensional Fourier transform rapid spin-echo (SE) technique. T1-weighted images (SE 500/28) showed a slight mass effect pushing the midline septum of the tongue to the left (Fig 1B), but T2-weighted images (SE 2,000/84) delineated a large high-signal lesion in the right side of the tongue, crossing the midline and extending to the floor of the mouth (Fig 1C). The enlarged right jugulodigastric node was also visualized on both MRI sequences.

The patient was subsequently treated with supervoltage irradiation over a period of 52 days in 35 fractions. The tongue and upper neck nodes bilaterally received a total of 55 Gy through opposed lateral portals, and the lower part of the neck received

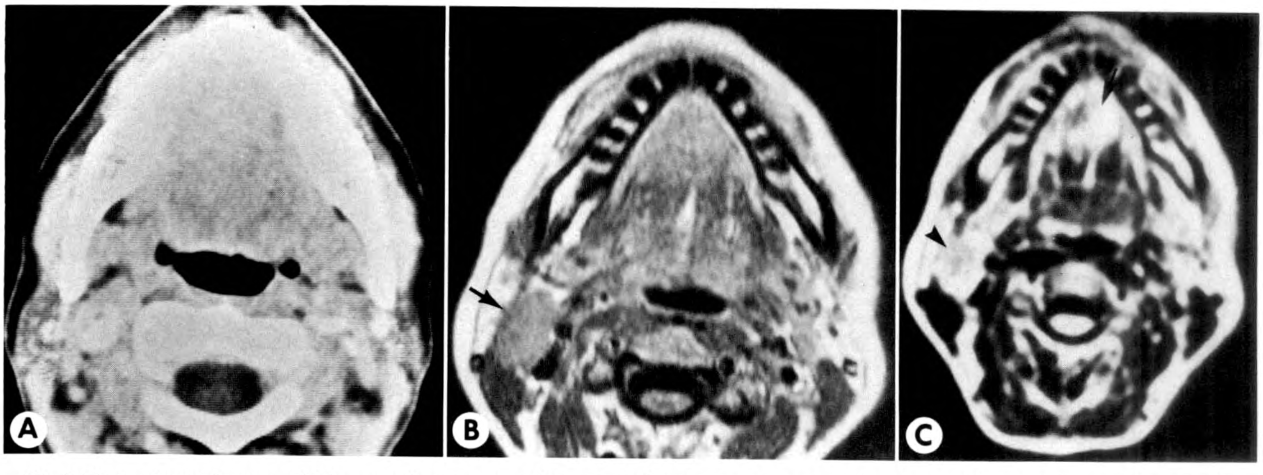

Fig 1. Pretreatment images. A) Computed tomogram of tongue with intravenous contrast shows no evidence of abnormality. B) T1-weighted (SE 500/28) magnetic resonance image at same level shows slight mass effect in anterior aspect of tongue, but it is otherwise unremarkable. Enlarged right jugulodigastric node is evident (arrow). C) T2-weighted magnetic resonance image (SE 2,000/84) at same level shows areas of high signal intensity delineating primary tumor and its extension into anterior floor of mouth (arrow), as well as abnormal lymph node (arrowhead).

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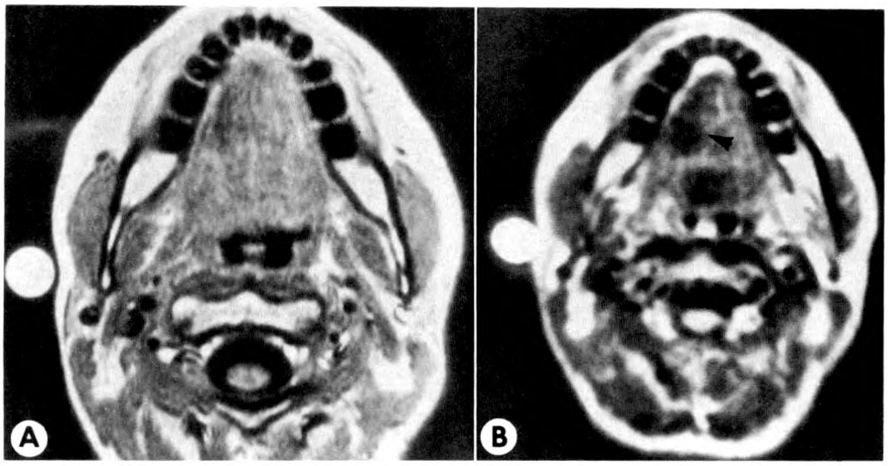

Fig 2. Posttreatment magnetic resonance images. A) T1-weighted image (SE 500/28) at same level as in Fig 1 now shows reduction of mass effect and minimal loss of signal in region of primary tumor, as well as decreased size of metastatic lymph node. B) T2-weighted image (SE 2,000/84) shows significant reduction in signal (arrowhead) with restoration of near-normal anatomy in tongue. Irregular areas of low signal within tongue may represent postirradiation fibrosis.

50 Gy through a single anterior portal. The enlarged right jugulodigastric node was given an additional boost with electrons for a *total* of 64 Gy. Thirteen iridium implants were then placed in the tongue, giving 35 Gy more to the area of the primary tumor. The pretreatment MRI scan (Fig 1C) helped to guide the placement of the implant needles.

Clinical examination after the completion of treatment showed the cervical node and the primary lesion to have regressed, with a corresponding increase in tongue mobility. However, an indurated area was still present in the right anterior aspect of the tongue, and it was not clear whether this represented fibrosis or residual tumor. Follow-up T1-weighted MRI performed 2 years after the completion of radiotherapy (Fig 2A) confirmed the reduction in mass effect within the tongue, as compared to the pretreatment study, with restoration of the midline septum to a normal position. T2-weighted images (Fig 2B) displayed areas of *low* signal intensity in the tongue and in the floor of the mouth, indicating considerable reduction in the T2 relaxation times in the region of the primary tumor. The involved upper cervical node was also reduced in size on both MRI sequences, and the patient is continuing to do well without evidence of recurrence 3½ years following completion of her treatment.

DISCUSSION

Computed tomography has come to be considered the imaging technique of choice to evaluate and stage oral cavity neoplasms; it is also thought by some to have a potential role in the early detection of malignancies in this region.[1,2] In our patient, CT failed on two occasions to delineate the primary tumor that was infiltrating the tongue and floor of the mouth.

The limitations of CT in this body region include beam artifacts that may arise from the mandible or from prosthetic devices and dental amalgam. Furthermore, the inherent contrast between normal tongue musculature and tumors on CT images is usually low, even with an intravenous contrast infusion.[3] The delineation of local tumor extent may depend on mass effects (eg, displacement of the midline septum) and/or obliteration or alteration of fatty planes in the surrounding musculature rather than on changes in tissue density.[3]

There are several potential advantages of MRI for diagnosing and staging tumors in this anatomic region.

1. Since cortical bone in the mandible does not produce an MRI signal, there are no bony artifacts to obscure detail on MRI images.

2. Amalgam, which is the most common dental filling material, contains silver, tin, and mercury, none of which degrades magnetic resonance images.[4] Other dental material such as crowns or bridgework *may* cause local MRI artifacts, but these are limited to the immediate area of the offending material and do not cause global degradation of the image as may occur with CT.[5]

3. The most important advantage of MRI is the inherently high tissue contrast between tumor and normal musculature on T2-weighted images (Fig 1C). While T1-weighted or proton density images may not show a significant difference in signal between muscle and tumor, they may afford more precise anatomic definition with a larger tumor and may help to evaluate the relationships between the tumor and surrounding fatty planes.[6,7]

4. The ability of MRI to produce direct images in sagittal, axial, and coronal planes may also have advantages for recognizing the relationships between a tumor and the intrinsic tongue musculature, the midline septa, and the vascular and nervous pathways for purposes of staging and treatment planning.[5] The multiplanar imaging capability may be especially helpful when a limited surgical resection of the tongue is being considered, since this requires preservation of at least one lingual artery and hypoglossal nerve.[8]

The main shortcoming of MRI (which also applies to CT) in the pretreatment evaluation of tongue malignancies is the difficulty that may be encountered in differentiating tumors from normal lingual tonsils: oral tumors and normal lymphatic tissue have similar signal intensities on T1- as well as on T2-weighted images.[5] While normal lingual tonsils sometimes appear to be asymmetric, they usually do not exhibit the deep tissue infiltration on cross-sectional images that may be associated with a carcinoma. Accordingly, a knowledge of the normal anatomy, and especially of normal variants in the oral lymphoid structures, is necessary to avoid misinterpretations in the region of the tongue base and floor of the mouth.

The interpretation of posttreatment follow-up studies with MRI, as well as with CT, may prove difficult. While postirradiation fibrosis or scarring tends to exhibit a lower signal intensity on T2-weighted images than persistent tumor in the tongue,[9] inflammatory changes, posttreatment edema, and/or tumor may all exhibit high signal intensity in these sequences.[10] *Increasing* signal intensities or persistent high signal levels on serial T2-weighted studies after treatment may suggest recurrent or persistent tumor. The delayed posttreatment imaging study in our patient exhibited no areas of high signal on T2-weighted images, and it was concluded that she was probably free of local tumor. This has been confirmed subsequently by her clinical course.

The currently reported case illustrates the superior sensitivity of MRI over CT for evaluating carcinomas of the tongue, because of the high soft-tissue contrast that can be obtained with T2-weighted images. Therefore, MRI now appears to be the preferred imaging modality for evaluating tongue neoplasms prior to and following treatment.

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XX INTERNATIONAL CONGRESS OF AUDIOLOGY

The XX International Congress of Audiology will be held October 14-18, 1990, in Tenerife, Canary Islands, Spain. For further information, contact Dr Jose Barajas, Presidente, C/Perez de Rozas, 8, 38004 Santa Cruz de Tenerife, Canary Islands, Spain; telephone 22 27 54 88; telex 91106.

Ann Otol Rhinol Laryngol 99:1990

PATHOLOGY CONSULTATION

SIALADENOMA PAPILLIFERUM

KAREN R. CLEARY, MD JOHN G. BATSAKIS, MD

HOUSTON, TEXAS

Sialadenoma papilliferum is a tumor of salivary tissues that has considerable histologic and biologic similarities to analogous tumors of the eccrine apparatus of the skin. Thus far found only at intraoral and parotid gland sites, sialadenoma papilliferum usually has the clinical course of a benign, locally significant lesion.

Sialadenoma papilliferum is a rarely encountered neoplasm of salivary duct origin with a rather strong predilection for the palate.[1,2] When it is tabulated in reports of series of minor salivary gland tumors, it accounts for less than 1% of the tumors, benign and malignant.[3]

Distinguished by its close morphologic resem-

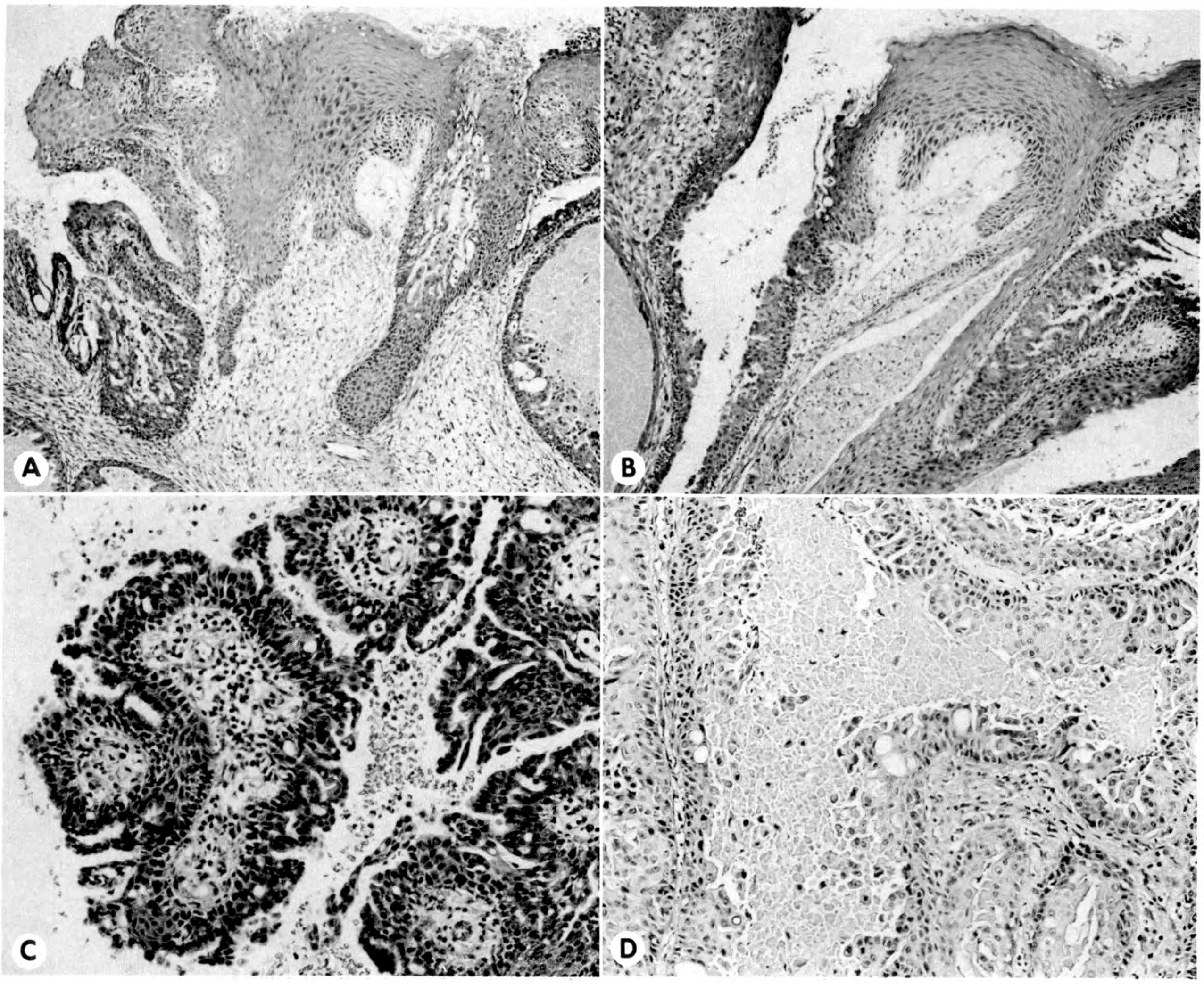

Fig 1. Sialadenoma papilliferum of palate. A) Surface area, with invaginations along excretory ducts and cystic dilatation of ducts (H & E, original x60). B) Verrucoid growth brought about by elongation of ducts, squamous metaplasia, and neoplastic proliferation of ductal epithelium (H & E, original x100). C) With papillary outgrowth to surface of ductal epithelium (H & E, original x180). D) Deep-lying duct (H & E, original x180). Note grumous intracystic contents and oncocytic change in duct cells.

From the University of Texas M. D. Anderson Cancer Center, Houston, Texas.

REPRINTS — John G. Batsakis, MD, Dept of Pathology, University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Blvd, Houston, TX 77030.

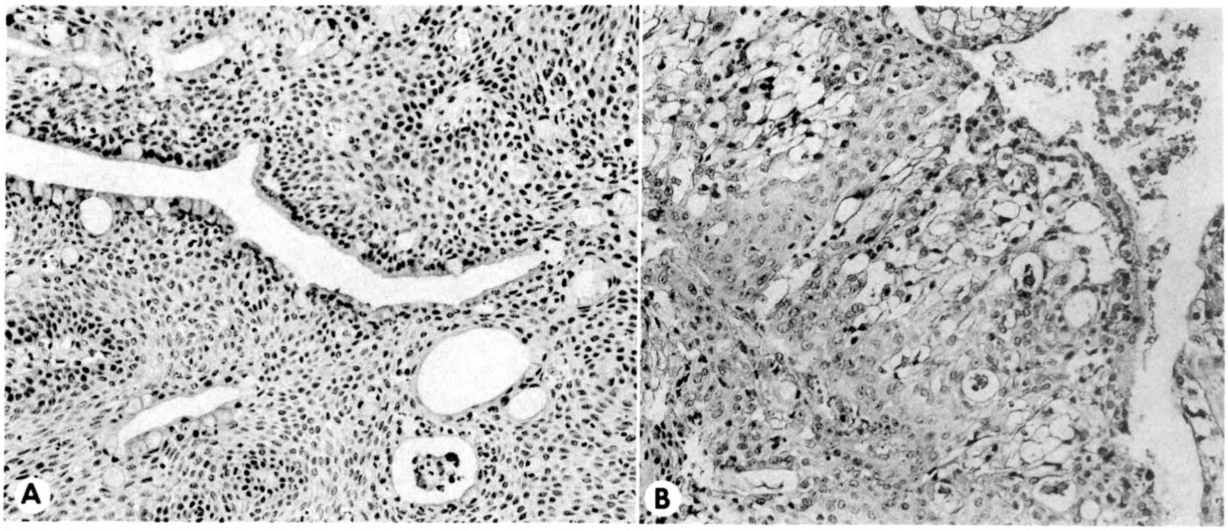

Fig 2. Two other intraoral neoplasms that also originate in salivary excretory ducts (H & E, original x160). A) Intraductal inverting papilloma of buccal mucosa. Note epidermoid cells, microcysts, and persistence of mucosal cells, all features not seen in sialadenoma papilliferum. B) Polypoid mucoepidermoid carcinoma composed of optically clear cells and intermediate cells.

blance to syringocystadenoma papilliferum of the skin's apocrine-eccrine sweat glands,[4] the diagnostic criteria for sialadenoma papilliferum have been, at times, so attenuated that other classifiable lesions have been included under its rubric.[1] Misclassification, low incidence, and short follow-up periods combine to make statements about the lesion's biologic behavior and its optimum management difficult to assess. Nonetheless, there is a contemporary opinion that sialadenoma papilliferum is a biologically benign tumor with limited potential for local aggressiveness. If extrapolation from the clinical behavior of syringoadenoma papilliferum is permitted, it would appear that transition to carcinoma is rare.[4]

The typical patient is male, older than 50 years, with a painless exophytic, papillary growth of the palate, often at the junction of the hard and soft palates. Other intraoral sites have been the buccal mucosa, retromolar fat pads, and lip.[1,2,5,6] Only two examples have been reported in the major salivary glands, both intraparotid.[7,8] A large size, as in the 7.5-cm mass reported by Abrams and Finck,[7] is unusual. The intraoral sialadenomas are most often less than 1.0 cm when discovered.

Sialadenoma papilliferum presents as a verrucoid, exophytic lesion whose cut surfaces tend to be multicystic. The microscopic appearance of the lesion is displayed in Fig 1. The lesion is broad-based, with an overlying parakeratotic, acanthotic squamous epithelium that is in continuity with elongated, at times tortuous, and dilated excretory salivary ducts. The squamous mucosa is interrupted by papillary fronds from the luminal surface of the ectatic ducts. In the lower portions of the lesions, the ducts are cystically dilated and contain cellular debris or secretory product. The stroma contains a variable density of chronic inflammatory cells, but never of the magnitude seen with syringocystadenoma papilliferum or Warthin's tumors. Minor salivary tissue may be involved, but never to the extent that histogenesis other than from the excretory ducts is suggested. The ducts and their papillary folds are often lined with a double row of cells: a basal layer of cuboidal and a luminal layer of taller, columnar cells. Squamous metaplasia, most often near the mucosal surface, is nearly always present. Oncocytic or mucous differentiation is variable and not always seen.

To date, the histologically verifiable sialadenomas papilliferum recorded in the literature have been biologically benign and rarely recurred after excision. A possible malignant analogue with metastasis to a cervical lymph node has been recorded by Solomon et al.[9]

Two other intraoral neoplasms that also take their origin from the salivary excretory ducts should not be confused with sialadenoma papilliferum. These are the inverted ductal papilloma and a preponderantly intraductal mucoepidermoid carcinoma.

The inverted duct papilloma closely resembles the schneiderian papillomas of the sinonasal tract both in growth pattern and cytoarchitecture.[10] Both contain mucous cells, microcysts, and luminal cells, which can be epidermoid, columnar, or cuboidal (Fig 2A). Clinically, the lesions are nearly always submucosal and present as 1- to 1.5-cm slow-growing nodules. The floor of the mouth, soft palate, mandibular vestibule, and buccal mucosa have been areas of origin. Simple excision is said to be curative, unlike with schneiderian papillomas.

The paucity of true squamous metaplasia, the presence of intermediate cells, and neoplastic, not hyperplastic, mucous or optically clear cells in mucoepidermoid carcinomas should allow for precise diagnostic separation of that carcinoma from sialadenoma papilliferum (Fig 2B).

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The 17th annual meeting of the American Auditory Society will be held November 15, 1990, in Seattle, Washington. For further information, contact Robert A. Dobie, MD, Chair, AAS Program Committee, Otolaryngology–Head and Neck Surgery, University of Washington RL-30, Seattle, WA 98195.

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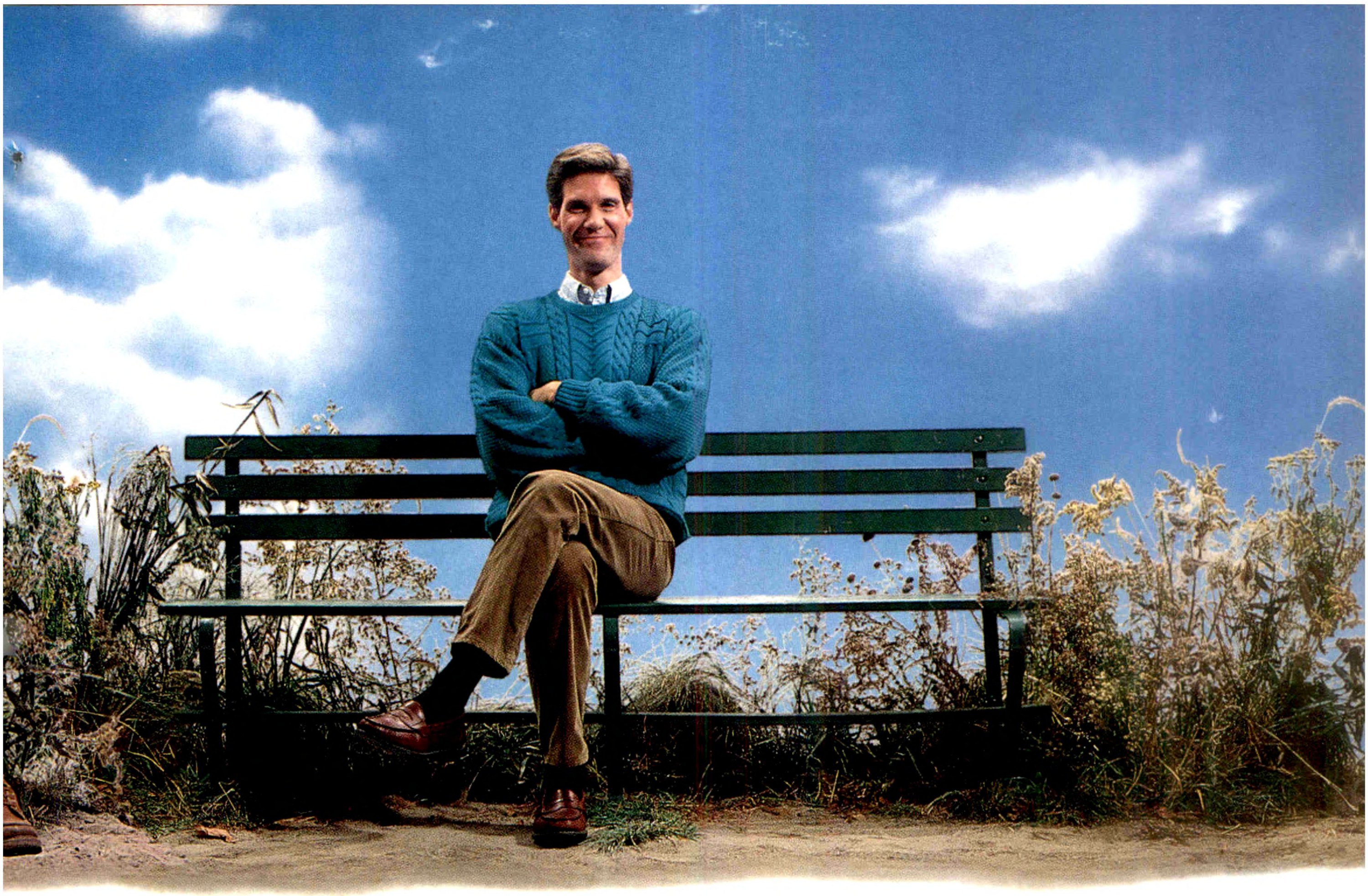

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Carcinogenesis, Mutagenesis, Impairment of Fertility: Treatment of rats for a total of 95 weeks, 13 weeks by inhalation and 82 weeks by the oral route, resulted in no evidence of carcinogenic activity. Mutagenic studies have not been performed.

Impairment of fertility, as evidenced by inhibition of the estrous cycle in dogs, was observed following treatment by the oral route. No inhibition of the estrous cycle in dogs was seen following treatment with beclomethasone dipropionate by the inhalation route.

Pregnancy: ***Teratogenic Effects: Pregnancy Category C:*** Like other corticoids, parenteral (subcutaneous) beclomethasone dipropionate has been shown to be teratogenic and embryocidal in the mouse and rabbit when given in doses approximately ten times the human dose. In these studies, beclomethasone was found to produce fetal resorption, cleft palate, agnathia, microstomia, absence of tongue, delayed ossification, and agenesis of the thymus. No teratogenic or embryocidal effects have been seen in the rat when beclomethasone dipropionate was administered by inhalation at ten times the human dose or orally at 1,000 times the human dose. There are no adequate and well-controlled studies in pregnant women. Beclomethasone dipropionate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects: Hypoadrenalism may occur in infants born of mothers receiving corticosteroids during pregnancy. Such infants should be carefully observed.

Nursing Mothers: It is not known whether beclomethasone dipropionate is excreted in human milk. Because other corticosteroids are excreted in human milk, caution should be exercised when Beconase (beclomethasone dipropionate, USP) Inhalation Aerosol or Beconase AQ Nasal Spray is administered to nursing women.

Pediatric Use: Safety and effectiveness in children below 6 years of age have not been established.

ADVERSE REACTIONS: In general, side effects in clinical studies with both preparations have been primarily associated with irritation of the nasal mucous membranes.

Extremely rare instances of wheezing, nasal septum perforation, and increased intraocular pressure have been reported following the intranasal administration of aerosolized corticosteroids (see PRECAUTIONS).

Rare cases of immediate and delayed hypersensitivity reactions, including urticaria, angioedema, rash, and bronchospasm, have been reported following the oral and intranasal inhalation and administration of beclomethasone.

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Localized infections of the nose and pharynx with *C albicans* have occurred rarely (see PRECAUTIONS).

Transient episodes of epistaxis have been reported in 2 per 100 patients. Ulceration of the nasal mucosa has been reported rarely.

Systemic corticosteroid side effects were not reported during controlled clinical trials. If recommended doses are exceeded, however, or if individuals are particularly sensitive, symptoms of hypercorticism, ie, Cushing's syndrome, could occur.

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OVERDOSAGE: Information concerning possible overdosage and its treatment appears in the full prescribing information.

RB2-1006 March 1989

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BSE 324
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Further information about the position and qualification requirements may be obtained by contacting Ms. Christine A. Clements at (301) 402-0508 (Voice or TDD) or TDD (301) 402-1134. An Application for Federal Employment (SF-171) along with a Curriculum Vitae and Bibliography should be submitted to:

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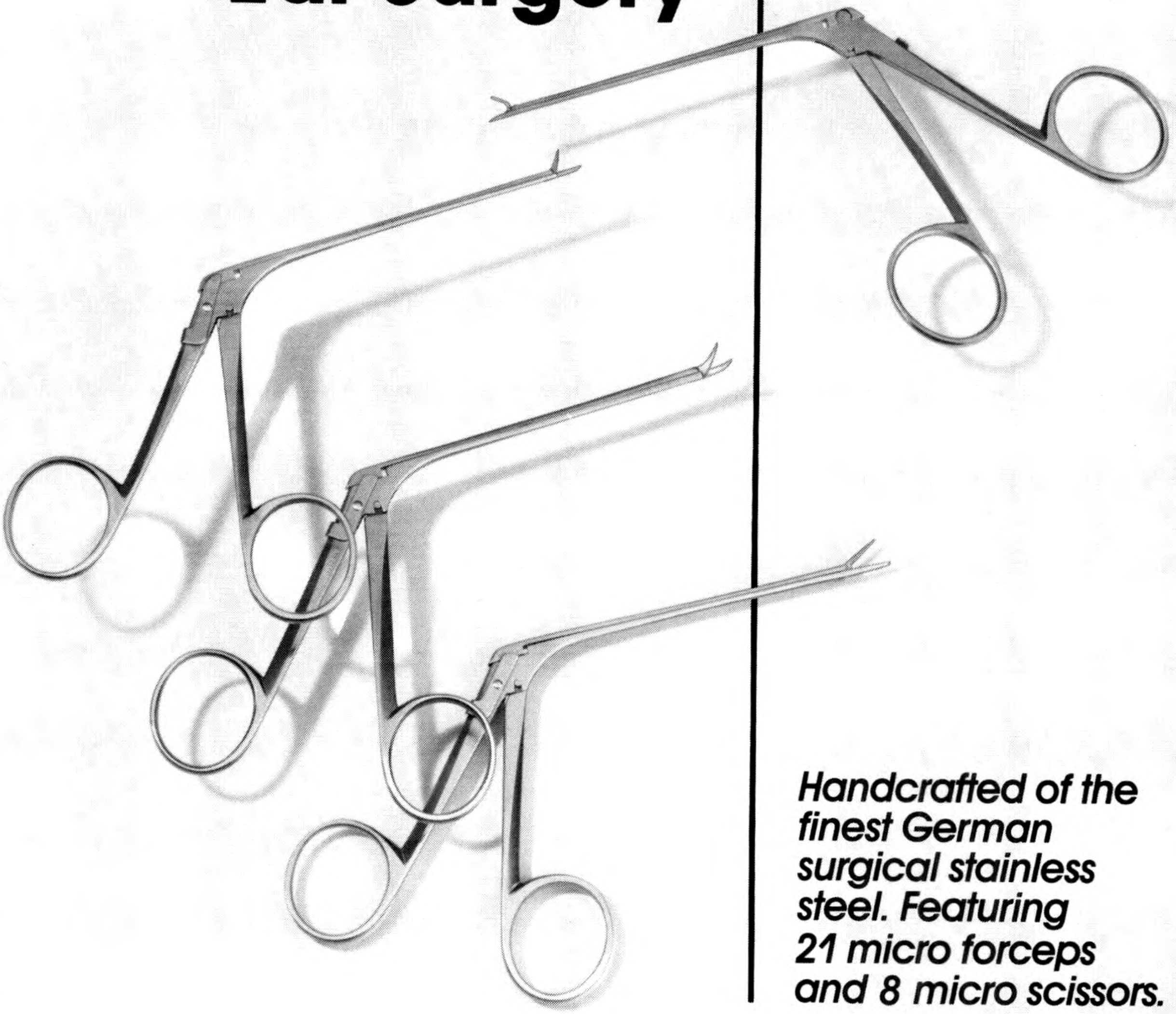

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Ann Otol Rhinol Laryngol 99:1990

TEFLON VERSUS THYROPLASTY VERSUS NERVE TRANSFER: A COMPARISON

ROGER L. CRUMLEY, MD

IRVINE, CALIFORNIA

Surgical rehabilitation of the paralyzed larynx is currently performed by Teflon injection, thyroplasty, and reinnervation techniques. Proponents of the two newer techniques maintain that they are preferred to Teflon injection because superior phonatory quality is achievable. This paper was written in an attempt to dissect the issues regarding this question. Teflon remains the quickest and least expensive procedure, but further experience with stroboscopic and other voice analyses reveals that the other procedures demonstrate some superiority in phonatory quality over Teflon. In this author's hands, the nerve transfer offers the best opportunity to achieve a normal phonatory voice. In addition, it is the only one of the three procedures that leaves the vocal cord entirely undisturbed — important in the event one of the other two procedures becomes necessary.

KEY WORDS — laryngoplasty, nerve transfer, reinnervation, Teflon injection, thyroplasty.

INTRODUCTION

Currently there are three techniques used clinically for treatment of patients with unilateral vocal fold paralysis: Teflon injection, thyroplasty (Isshiki type I), and reinnervation. This paper will discuss the relative efficacy, cost, reversibility, applicability, and other aspects of these techniques.

Teflon Injection. Teflon injection was introduced by Arnold[1] in 1962. The technique has been the standard treatment for vocal fold paralysis for approximately 30 years. It is relatively easy to perform, cost-effective, expeditious, and well tolerated. Complications are few and infrequent. If it were universally successful in restoring a satisfactory voice, it would clearly be the treatment of choice.

Thyroplasty (Laryngoplasty). The Isshiki type I thyroplasty was introduced in 1974 by Isshiki et al.[2] It was one of several types of procedures performed on the cartilaginous skeleton to effect changes in vocal cord position. The Isshiki type I procedure involves placing an alloplastic implant inside a window in the thyroid cartilage. The implant pushes the paralyzed vocal fold medially in a manner similar to the mechanism of Teflon injection. The Isshiki I thyroplasty is somewhat more difficult to perform than Teflon injection and also requires an incision in the neck. It is probably somewhat more expensive than Teflon injection, since the thyroplasty must be performed in the operating room (whereas some practitioners are now performing Teflon injection in an office setting). The advantages of thyroplasty are twofold. First, the procedure allows for "tuning" the amount of medialization of the vocal fold as determined by the quality of voice produced. (The patient is able to phonate under local anesthesia and the amount of medialization can be controlled by thinning or thickening the implant.) Second, the procedure is (at least theoretically) reversible. These advantages have led a handful of expert laryngologists in this country and Japan to prefer thyroplasty to Teflon injection. However, it has not achieved universal acceptance in this country at the time of this writing.

Nerve Transfer. Nerve transfer for laryngeal paralysis is perhaps the oldest of the three techniques, having first been reported by Frazier and Mosser[3] in 1926. More recently the neuromuscular pedicle was described for treatment of vocal fold paralysis by Tucker and Rusnov,[4] and subsequently Crumley and Izdebski[5] described initial results with ansa cervicalis (hypoglossi)–recurrent laryngeal nerve (RLN) anastomosis in 1986. Nerve transfer offers the theoretic advantage of reinnervating the paralyzed laryngeal muscles. Its disadvantages are that it requires a neck incision and takes slightly more time in the operating room; hence, it is more expensive. It is reversible. In our experience thus far in 20 cases, patients are very highly satisfied with the procedure (unlike many patients who have undergone Teflon injection).

COMPARISONS

Each of the three procedures will be discussed relative to several parameters that allow comparisons.

Time. When performed in the operating room, Teflon injection ordinarily takes 30 to 45 minutes, depending on local anesthesia time, patient positioning, etc. Those surgeons who prefer general anesthesia probably take slightly longer.

The type I thyroplasty in our university hospital takes approximately 45 to 90 minutes. Surgeons

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with a wider experience with thyroplasty report that it is possible to reduce the operating time to 30 minutes. However, our operating time for the procedure is comparable to that of most other surgeons.

The ansa cervicalis transfer technique averages just under 2 hours. If there is difficulty in locating a scarred or transected RLN, it can take longer.

Ease of Performance. This comparison is difficult, insofar as surgeons' expertise, technical capabilities, and experience differ widely. Certainly the ease of Teflon injection is directly proportional to the surgeon's experience. There are several successful methods that can be used in Teflon injection. Our preference is to perform the procedure via indirect laryngoscopy with the patient in the sitting position under local anesthesia in the operating room. Other surgeons use the local anesthesia–direct laryngoscopy technique (supine position), while others prefer general anesthesia and the supine position. Ward et al[6] and McCaffrey and Lipton[7] use a fiberoptic endoscope to observe the larynx while the Teflon is injected percutaneously. This is done in a clinic setting rather than the operating room. No matter which technique is used, Teflon injection is ordinarily not associated with any great degree of technical difficulty.

Thyroplasty under local anesthesia is a relatively easy procedure — somewhat more difficult than Teflon injection, and perhaps slightly simpler than nerve anastomosis. When the thyroid cartilage is calcified, it requires a small drill or an oscillating saw to make the window.[8] We routinely observe the vocal fold through a fiberoptic laryngoscope at the time of positioning the implant. This occasionally creates some minor logistic difficulties in the operating room. (Sasaki et al[9] have abandoned endoscopic examination during implant placement, preferring to use vocal quality as the determinant for implant positioning and thickness.) Although sculpting of the implant can take time, it is not a difficult procedure. The infrathyroid muscles are usually transected and subsequently repaired, but this step adds little to the difficulty involved with the procedure.

The ansa cervicalis–RLN anastomosis is also an uncomplicated surgical procedure. The ansa cervicalis (formerly hypoglossi) is identified under the fascia overlying the internal jugular vein. The distal portion of the nerve divides into two branches: one to the sternohyoid muscle, and the other to the sternothyroid. Any difficulty associated with the procedure generally comes from identification of the RLN, particularly if the neck has been previously operated upon. The nerve anastomosis is generally done with the operating microscope and three to four 10-0 monofilament nylon sutures.

Time Interval to Improvement. Phonatory improvement from Teflon paste injection is generally immediate. Approximately one half of the injected material is composed of glycerin, and this is absorbed in the first few weeks following injection. However, the medialized vocal cord begins to function as an improved vibratory mate for the normal cord immediately after injection.

Thyroplasty is similarly an immediate correction of the vocal fold lateralization resulting from paralysis. The implanted Silastic block pushes the vocal fold medially and allows the patient to phonate immediately (on the operating table) with the newer mechanism. We have found that if the procedure takes longer than a half hour, edema of the vocal fold and paraglottic tissues may occur because of the necessary minor surgical trauma, and this edema may result in placement of a slightly smaller implant than is desirable — a problem described by Isshiki et al[8] in a recent communication. In this scenario there may be a slight loss in vocal quality as this edema clears. This finding prompted Isshiki et al[8] to advise "overmedialization" — further indication to this author that thyroplasty is not the exact and precise procedure that it was initially thought to be.

Nerve transfer has two increments of vocal improvement. The first is usually immediate and is thought to be secondary to sternothyroid muscle denervation that results from ansa cervicalis transection. The main phonatory improvement, however, takes 2½ to 3 months following the procedure, during which time the axons grow through the nerve anastomosis and traverse the distal stump of the RLN to reach the paralyzed laryngeal muscles. We frequently inject Gelfoam paste in the ipsilateral cord to provide the patient with the advantages of immediate improvement during the early portion of the 2- to 3-month interval during which reinnervation occurs.[5]

Reversibility. Teflon injection is essentially irreversible. Once the Teflon bolus has been placed in the paraglottic space or substance of the vocal cord, it becomes fixed into position by fibrous tissue.[10] Although one may vaporize a certain amount of injected Teflon with the carbon dioxide laser, this procedure is not possible without some associated injury to the vocal cord structure. This is perhaps the biggest disadvantage of Teflon injection. Horn and Dedo[11] described removal of Teflon via an incision in the floor of the ventricle, but felt that the procedure was not exact. The safety of laser removal of Teflon was questioned in a study by Koch et al.[12] These investigators found Teflon to be inflammable initially, but after 7 weeks it was found only to "glow," and they believed that laser removal was probably safe then. This belief has proven to be clinically true.

Thyroplasty is theoretically reversible. By simply removing the Silastic implant, one could permit the paralyzed vocal fold to move laterally to its former position as the perichondrium reattaches to its former position along the internal border of the thyroid cartilage. Total reversibility, however, is probably not possible, insofar as there would be some scarring around the implant and the vocal cord tissues (vocalis muscle, conus elasticus, thyroarytenoid muscle) might not completely lateralize to their former position following removal of the implant. Isaacson et al[13] described atrophic changes of the cord structures, with fibrous capsule formation around the implant. The depressed cartilage showed greater anterior than posterior displacement.

Theoretically, ansa cervicalis–RLN anastomosis is completely reversible. Although we have not had to reverse it in any of our first 20 patients, it would not be a difficult surgical procedure to reexplore and transect the nerve anastomosis, the distal RLN, or the ansa cervicalis proximally. We have found via laryngeal electromyography that most patients with "vocal cord paralysis" have some reinnervation of the laryngeal muscles. Accordingly, if nerve transfer is performed for one of these patients with partial reinnervation and synkinesis, the vocal cord muscles and structure would not return to the preanastomosis state (synkinesis) following transection of the nerve anastomosis. Rather, the laryngeal muscles would probably be totally paralyzed rather than being synkinetic. Since synkinesis could produce slight tonic abduction of the arytenoid (or adduction, for that matter), vocal quality following reversal would be unpredictable. Certainly Teflon injection and/or thyroplasty could be performed subsequently (to further medialize the cord), although that has been necessary in only two of our cases to date.

Changes in Vocal Cord Structure. Teflon injection results in placement of a bolus of Teflon paste in the lateral portion of the vocal fold and/or paraglottic space. The Teflon is surrounded by capillaries and fibrous tissue and becomes incorporated into the vocal cord.[10] Since approximately half of the injection is absorbed (the glycerin), it is impossible to know exactly the correct amount to inject. The anatomy of the vocal fold is irreversibly altered. The author and other surgeons have "removed" Teflon with the carbon dioxide laser, but this procedure produces an additional injury. (See Reversibility, above.)

Type I thyroplasty also changes the actual vocal cord structure. Operating through the window in the thyroid cartilage, the surgeon is looking at and manipulating the lateral portion of the paraglottic space and internal perichondrium. It is necessary to use electrocautery on occasion, producing additional injury. Although removal of the implant may allow the vocal cord structure to return to its preoperative state, it is possible that the vocal cord structure will have been permanently altered.[12]

Ansa cervicalis–RLN anastomosis does not alter the vocal cord structure, since the larynx is not entered at all in the procedure. The only structural change results from the normalization of muscle bulk and resulting vocal cord compliance following passage of the reinnervating ansa cervicalis axons into the endolaryngeal muscles.

Complications. Teflon injection complications are uncommon. However, migration of the substance into the thyroid gland can mimic a cold thyroid nodule. Overinjection of the cord can result in airway distress and can precipitate the need for tracheotomy. Another reported complication is Teflon granuloma.[14] Perhaps the most common complication is overinjection. The author has removed Teflon from the free edge of the true cord on several occasions without encountering delayed healing or granuloma formation, but improvements in phonatory quality have been minimal.

Thyroplasty complications are generally minimal. Bleeding from the perichondrium and/or muscles is not infrequent during the procedure, but is usually self-limited. Infections are theoretically a problem, but the larger series report little difficulty in this regard. Hematoma formation requiring tracheotomy, and implant slippage necessitating reoperation with replacement of the implant have been reported.[15] Difficulties with overmedialization and undermedialization were reported by Maves et al.[15] Isshiki et al[8] recently described the necessity for overmedializing the vocal cord for best results, and this practice will probably increase the airway complications reported with the procedure. We have not yet experienced these complications, but presumably will as the series grows.

Ansa cervicalis–RLN anastomosis also has relatively few complications. Because of the dissection along the trachea, hematomas and bleeding are slightly more likely with this procedure than with thyroplasty. Infection is theoretically a greater risk for the same reasons. However, we have not experienced an infection in our first 20 cases. We had to take one patient back to the operating room for postoperative bleeding (the only patient in our series who was operated on at the Veterans Administration hospital).

Applicability and Indications. Teflon injection is nearly universally applicable in vocal fold paralysis. It is contraindicated in bilateral cases or when the movement of the opposite cord is otherwise impaired. However, for aspiration or for phonatory improvement from unilateral vocal fold paralysis, it is the most expeditious and commonly performed procedure.

Thyroplasty is slightly more limited than Teflon injection, insofar as the patient must be capable of undergoing an open surgical procedure in the operating room. However, since it is done under local anesthesia and takes approximately an hour, there are relatively few medical contraindications to the procedure.

Ansa cervicalis–RLN anastomosis is slightly more limited in applicability when compared with the other two procedures in management of vocal fold paralysis. If there is no distal RLN stump available, the procedure cannot be done. The prime candidates are those with injuries to the cervical vagus nerve or the intrathoracic RLN, since the cervical RLN is intact. In those patients who have had injuries to the RLN in the neck such as those following thyroidectomy, one can expect an increased amount of difficulty in identifying the RLN and in mobilizing an appropriate distal stump to which to suture the ansa cervicalis. In our series this has been a problem in only one patient. In such cases it is sometimes most expeditious to find the RLN distal (superior) to the thyroid gland region under the anterior-inferior corner of the thyroid ala immediately deep to the attachments of the inferior constrictor. Because increased difficulty should be anticipated in patients with upper RLN injuries, it may be helpful for a surgeon who wishes to learn this technique to select a patient with an intrathoracic or cervical vagal injury for his or her first case.

We have employed electromyography in selected cases to determine whether the sternothyroid muscle is normally innervated. This technique is also useful in evaluating the state of innervation or reinnervation of the endolaryngeal muscles. To date, however, the only contraindications to the technique in our hands are 1) advanced age (over 70); 2) a patient too ill or infirm for general anesthesia; 3) terminal cancer patients (or others who need immediate prevention of aspiration; Gelfoam paste injection may be used in addition to nerve transfer for short-term alleviation of aspiration); 4) other nerve injuries (contralateral RLN or superior laryngeal nerve); and 5) prior Teflon injection (a relative contraindication).

Our current indications for type I thyroplasty are 1) refusal of Teflon injection and 2) no distal RLN or available ansa cervicalis (precludes ansa transfer procedure).

Cost. Since thyroplasty is not yet performed by every laryngologist, and the nerve transfer procedure is likewise unfamiliar to many, it is difficult to make valid conclusions about the relative surgical costs for the procedures. In this regard the author contacted several surgeons who are currently using the Isshiki type I thyroplasty. It was ascertained that surgical fees for thyroplasty run approximately 60% additional over those for Teflon injection via direct laryngoscopy. Nerve transfer was approximately 100% additional (double) the cost for Teflon injection. Thyroplasty and nerve transfer are additionally more expensive because of operating room fees. It has been our routine to hospitalize patients overnight following nerve transfer because of the dissection in the tracheoesophageal groove and the need for a surgical drain.

Success (Phonatory Improvement). In our hands nerve transfer clearly produces the best results, if the goal of operation is a normal voice. Videostroboscopic analysis has greatly improved our abilities to analyze voices and larynges. It is probably not coincidence that the current fascination with noninjection techniques has accompanied the development of laryngeal stroboscopic examinations, glottographic analysis, photoglottography, and other modern voice analyses.

Teflon seldom if ever allows for a normal mucosal waveform from the injected vocal cord. The globule of paste pushes the paralyzed atrophic thyroarytenoid muscle and other vocal fold structures medially, further exaggerating the asymmetry that exists between the vocal folds. The injected cord's decreased compliance makes it a "passive partner" because of increased stiffness.[16] Most sound (fundamental frequency, etc) is generated from the contralateral normal cord. This may in fact explain the vocal fatigue that many Teflon-injected patients describe.

Thyroplasty is held by many as an improvement over Teflon injection because of improved subjective vocal quality and results on stroboscopic analysis.[16] To date, our own thyroplasty patients have not demonstrated a "nearly normal" voice, while this has become the expected result with ansa-RLN anastomosis.

SUMMARY

In summary, Teflon injection, thyroplasty, and laryngeal reinnervation via nerve transfer are all used for surgical rehabilitation of laryngeal paralysis. Teflon injection clearly is the most cost-effective and expeditious. It has been proven over several decades to provide relief from the vocal disability and aspiration that often result from the paralysis of one vocal fold. Wider usage of laryngeal videostroboscopy has confirmed that there are problems in speech rehabilitation from Teflon injection.

Isshiki type I thyroplasty provides another means of medializing a paralyzed vocal fold, and offers the advantage of reversibility when compared with Teflon. Surgeons with the greatest experience with thyroplasty report that its phonatory results are superior to those with Teflon injection. Other surgeons have been unable to routinely achieve excellent phonatory results with the technique and have reverted back to Teflon injection as the mainstay in treatment. The author currently prefers Teflon to thyroplasty for those patients who are not candidates for nerve transfer.

Ansa cervicalis–RLN anastomosis offers advantages over the other procedures, namely restoration of muscle tone to the paralyzed endolaryngeal (intrinsic) muscles. Restoration of muscle tone in turn results in more normal compliance of the vocal fold, stabilization of the arytenoid and vocal process, and ability of the glottis to produce symmetric mucosal waveforms in both vocal folds. Nerve transfer, like thyroplasty, is reversible. The reinnervated vocal fold may be injected with Teflon, Gelfoam, or other substances following nerve transfer, if vocal cord positioning or voice is not satisfactory following reinnervation.

The author's experiences with the three procedures indicate that nerve transfer offers the greatest chance for normal vocal quality, and that it is indicated for younger patients or those with professional uses of the voice, since the other two techniques may be reserved in the unlikely event of failure. Teflon injection remains the treatment of choice for the infirm or elderly requiring immediate vocal fold medialization.

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PAN AMERICAN ASSOCIATION OF OTORHINOLARYNGOLOGY–HEAD AND NECK SURGERY

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Ann Otol Rhinol Laryngol 99:1990

ENDOSCOPIC LASER ARYTENOIDECTOMY REVISITED

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Arytenoidectomy is currently the most reliable method of treating patients with bilateral vocal cord paralysis. Although both endoscopic and external approaches have been described, the endoscopic laser technique is more desirable because it requires no incision and allows for the immediate assessment of airway size. Eleven patients with bilateral vocal cord paralysis treated by endoscopic laser arytenoidectomy were presented in 1984. At that time, 10 of the 11 patients had been successfully decannulated. Follow-up on that group of patients revealed that 7 of the 10 successfully treated patients remain decannulated with a good airway, although 2 of these patients required a revision procedure to excise a granuloma. One patient failed at 15 months and has failed two subsequent revision operations, and 2 patients have been lost to follow-up. Since 1984, 17 additional patients with bilateral vocal cord paralysis have been treated by the authors using the same endoscopic laser arytenoidectomy technique; all have been successfully managed, with a minimum follow-up of 3 years. The technique of this operation will be reviewed. This study demonstrates the clinical usefulness of endoscopic laser arytenoidectomy in the treatment of bilateral vocal cord paralysis.

KEY WORDS — arytenoidectomy, endoscopy, laser, paralysis, vocal cord.

INTRODUCTION

The treatment of patients with bilateral vocal cord paralysis presents a challenge to the otolaryngologist–head and neck surgeon because of the "great compromise" associated with the surgical management of this condition. Many techniques have been proposed to manage individuals with bilateral vocal cord paralysis in an attempt to improve the patient's airway insufficiency without leaving him or her with a breathy, weak voice or an incompetent larynx. Most of these techniques, however, have resulted in a compromise, yielding an improved airway at the sacrifice of an understandable speaking voice.

Arytenoidectomy is currently the most reliable method of treating patients with bilateral vocal cord paralysis. Although both endoscopic and external approaches have been described, the endoscopic technique is more desirable because it requires no incision and allows for the immediate assessment of airway size. However, this technique has been historically difficult for many surgeons to master because of the intraoperative bleeding and edema that frequently occurred while they were manipulating microsurgical instruments through the operating microlaryngoscope.

Application of the carbon dioxide (CO_2) laser to the management of patients with bilateral vocal cord paralysis has facilitated certain refinements and afforded significant reproducibility to the technique of endoscopic arytenoidectomy. Specifically, use of the CO_2 laser has allowed the otolaryngologist–head and neck surgeon to perform precision operations through the relatively narrow field of the microlaryngoscope without the need for tissue manipulation. Additional advantages associated with the use of the CO_2 laser have included increased hemostasis and decreased intraoperative and postoperative edema.

This paper revisits a series of 11 patients with bilateral vocal cord paralysis who had been treated by endoscopic laser arytenoidectomy using a technique developed and subsequently modified by the two senior authors (R.H.O., G.A.S.) and presented in 1984.[1] At that time, 10 of the 11 patients had been successfully decannulated. Follow-up on that group of patients revealed that 7 of the 10 successfully treated patients remain decannulated with a good airway, although 2 of these patients required a revision procedure to excise a granuloma. One patient failed at 15 months and has failed two subsequent revision operations, and 2 patients have been lost to follow-up. Since 1984, 17 additional patients with bilateral vocal cord paralysis have been treated by the authors using the same endoscopic laser arytenoidectomy technique; all have been successfully managed, with a minimum follow-up of 3 years. The technique and potential problems of this operation will be reviewed.

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Presented at the meeting of the American Laryngological Association, Palm Beach, Florida, April 28-29, 1990.

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HISTORICAL REVIEW

The contemporary surgical and currently investigational treatment options for patients with bilateral vocal cord paralysis include tracheotomy, extralaryngeal arytenoidectomy, endoscopic arytenoidectomy, laryngeal reinnervation, endoscopic laser arytenoidectomy, endoscopic laser lateralization, functional electrical stimulation, and endoscopic laser posterior cordectomy.

Historically, tracheotomy was the only procedure available to the otolaryngologist–head and neck surgeon to treat the patient with bilateral vocal cord paralysis. In 1922, Chevalier Jackson[2] introduced a surgical technique that excised the entire vocal cord and ventricle; this procedure created an excellent airway, but the patient acquired an extremely breathy voice as a trade-off.

Hoover[3] presented the method of submucous resection of the vocal cord for the treatment of the patient with bilateral vocal cord paralysis in 1932. Failure resulted from this technique because of the severe postoperative dyspnea experienced by his patients. Laryngoscopy revealed excessive scar tissue formation that narrowed the glottis.

In 1939, King[4] proposed a new procedure that mobilized the arytenoid cartilage through an extralaryngeal, lateral approach. The anterior belly of the omohyoid muscle was cut and the arytenoid cartilage was sutured to its cut end. At first, the success of this procedure was thought to be secondary to physiologic restoration of vocal cord function by this omohyoid muscle transfer. However, it was later determined that the mobilized arytenoid cartilage became frozen in the abducted position secondary to fibrosis and scarring. Consequently, the omohyoid muscle transfer was later eliminated from King's operative procedure.

Kelly[5] introduced a slight modification of the King procedure in 1941 by dissecting and excising the arytenoid cartilage through a small window in the thyroid cartilage. This technique resulted in scar tissue formation that, in turn, caused the vocal cord to become abducted. Because the position of the vocal cord was not satisfactory in all cases, Kelly modified his own technique by securing the vocal cord in the abducted position by placing a lateralizing suture. In 1944, Orton[6] presented further minor modifications in the placement of this lateralizing suture.

In 1946, Woodman[7] reported a technique for the management of patients with bilateral vocal cord paralysis that maintains its popularity today. He exposed the arytenoid cartilage by separating the cricothyroid joint between the cricoid cartilage and the inferior cornu through a posterior-lateral approach. Following this exposure, he excised the arytenoid cartilage but preserved the vocal process, which he lateralized using a submucosal suture placed around the vocal process and anchored to the inferior cornu of the thyroid cartilage.

Thornell[8] described the first arytenoidectomy technique performed by an endoscopic approach in 1948. This report represented a significant advance in the management of patients with bilateral vocal cord paralysis. After first performing a tracheotomy, Thornell dissected free and excised the arytenoid cartilage through exposure gained by using the Lynch suspension laryngoscope. The surgical bed was electrocoagulated following removal of the arytenoid in an attempt to stimulate scar tissue formation and further lateralization of the vocal cord. The first large series of patients managed by the Thornell endoscopic arytenoidectomy technique was presented by Whicker and Devine[9] in 1972. These authors performed an endoscopic arytenoidectomy on 147 patients with bilateral vocal cord paralysis and were successful in relieving airway obstruction in 82% of their patients.

In 1953, Scheer[10] first described an anterior thyrotomy approach to perform an arytenoidectomy and lateralization procedure. The advantage of this technique was that it afforded the surgeon direct visualization for the exact placement of the vocal cord. Downey and Kennon[11] presented 12 patients in 1968 on whom they had performed the Scheer procedure with minor modification. Helmus,[12] in 1972, introduced the microsurgical thyrotomy approach to perform an arytenoidectomy, employing the binocular magnification and illumination offered by use of the operating microscope.

The nerve-muscle transposition operation was introduced by Tucker[13] in 1976, with subsequent progress reports being presented in 1978,[14] 1980,[15] and 1982.[16] Tucker transposed a nerve-muscle pedicle composed of the branch of the ansa hypoglossi that innervated the anterior belly of the omohyoid muscle to the posterior cricoarytenoid muscle via a posterior-lateral approach similar to that used to perform the Woodman operation. Others who have reported good results with this operation include Applebaum et al[17] and May et al.[18] In separate reports in 1982, Crumley[19] and Rice[20] described reinnervating the posterior cricoarytenoid muscle with phrenic nerve fibers that were split into a free nerve graft and anastomosed to the tiny abductor branch of the recurrent laryngeal nerve.

Strong et al,[21] in 1976, were the first to mention the use of the CO_2 laser for endoscopic arytenoidectomy, although they did not describe their actual technique or any attendant morbidity associated with this procedure. Eskew and Bailey[22] reported on their research using the CO_2 laser to perform endoscopic arytenoidectomies in dogs in 1983. They concluded that the laser was a useful surgical tool when applied in the management of bilateral vocal cord paralysis. Also in 1983, Ossoff et al[23] reported their preliminary experience with four patients with bilateral vocal cord paralysis treated by endoscopic laser arytenoidectomy; three of the four patients were successfully managed in this small series.

Zealear and Dedo[24] in 1977 demonstrated experimentally that electrical stimuli could trigger the laryngeal muscles. Experimental attempts at functional electrical stimulation were subsequently presented by Broniatowski et al,[25] Otto and Davis,[26] and Sanders et al[27] in 1986.

In 1985, Remsen et al[28] presented another endoscopic laser technique for the management of patients with bilateral vocal cord paralysis. They performed unilateral endoscopic laser excision of the thyroarytenoid muscle combined with suture lateralization of the vocal ligament and were successful in 13 of 14 patients. During that same year, Singer et al[29] discussed their experience performing arytenoidectomy without lateralization of the vocal cord through a thyrotomy approach. Eight of 9 patients were successfully decannulated in their series.

In 1989, Amedee and Mann[30] reported on a modification of the Clerf[31] arytenoidopexy procedure. The posterior cricoarytenoid and interarytenoid muscles were completely divided by an external approach. The arytenoid was mobilized, tilted laterally, and fixed into position by use of two or three permanent retention sutures. All 18 patients in their series were successfully managed with their technique.

Also in 1989, Dennis and Kashima[32] introduced the technique of endoscopic laser posterior cordectomy for the management of patients with bilateral vocal cord paralysis. They reported six cases with follow-up ranging from 1 year 10 months to 5 years 8 months. All patients in their series did well and none required a tracheotomy. The voice quality was reported to be subjectively good.

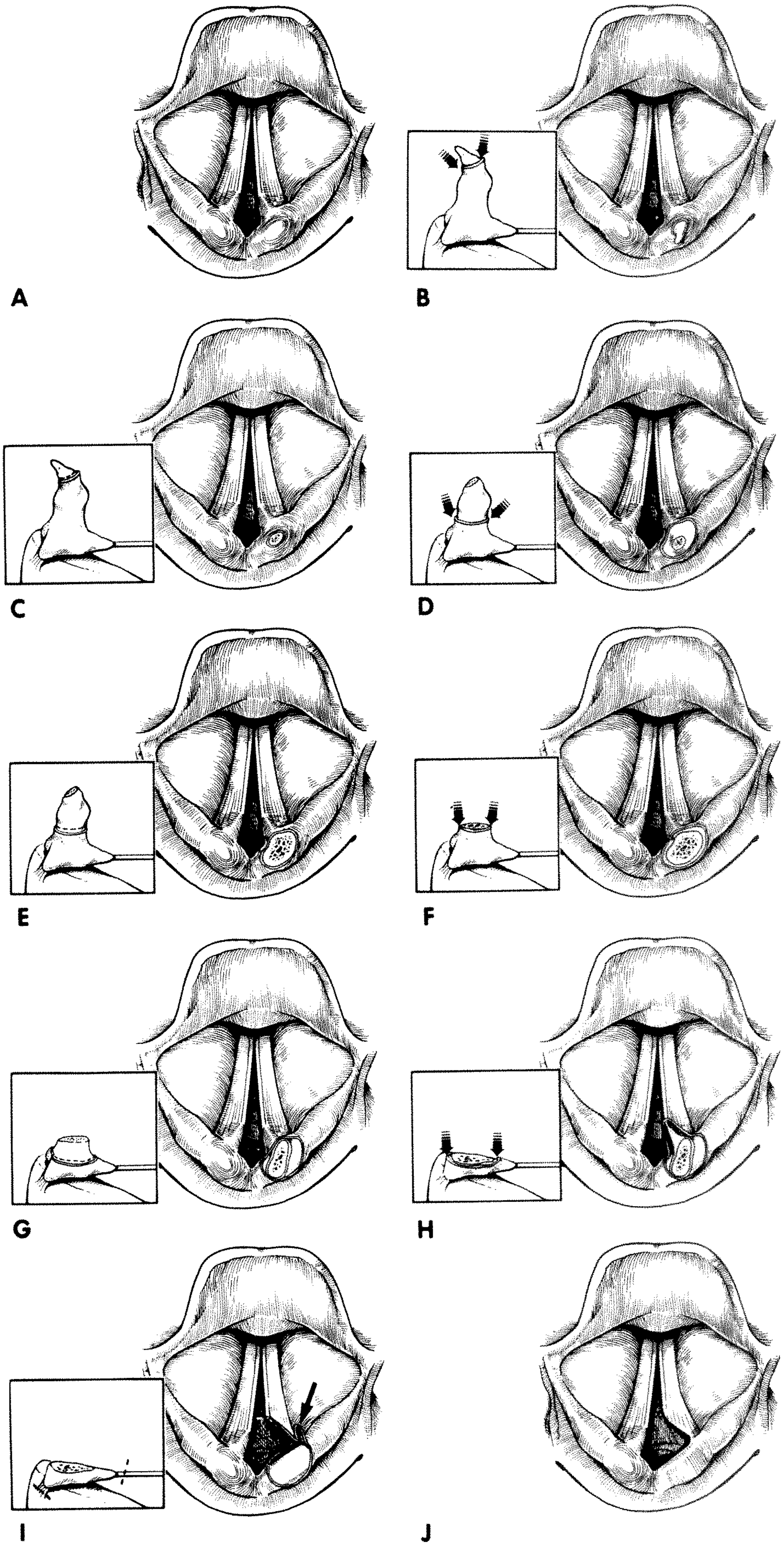
MATERIALS AND METHODS

First Series. Eleven patients with bilateral vocal cord paralysis were treated by endoscopic laser arytenoidectomy prior to 1984. Six patients in this series had indwelling tracheotomies at the time of presentation to us; two patients in this group were nerve-muscle transposition failures. The other five patients presented with compromised airways and had tracheotomies performed immediately prior to the laser arytenoidectomy procedure.

Second Series. Since 1984, 17 additional patients with bilateral vocal cord paralysis have been operated on by the authors. In this second series of patients, 11 had indwelling tracheotomies at the time of presentation to us. Five of the other 6 patients underwent tracheotomy immediately prior to the laser arytenoidectomy procedure. One patient in the second series did not undergo tracheotomy prior to the endoscopic laser arytenoidectomy procedure.

Surgical Technique. The surgical procedure used in all cases in both series was the same as that described in 1984[1] and resulted from a major modification of the Thornell endoscopic arytenoidectomy technique. The larynx was exposed with either the Ossoff posterior commissure laryngoscope[33] or the Ossoff-Karlan modified Dedo laryngoscope[34] (see Figure, A). Positioning of the laryngoscope was performed to facilitate complete exposure of one arytenoid cartilage, the posterior commissure and interarytenoid cleft, and at least half of the other arytenoid cartilage. Most often, the right arytenoid was more easily exposed in its entirety than the left. The authors routinely pass a 5.0- or 5.5-mm red rubber endotracheal tube wrapped with metallic reflective tape to separate the vocal cords and facilitate more working room in the posterior commissure. The groove on the posterior commissure laryngoscope holds the endotracheal tube anteriorly out of the way.

All procedures were carried out with a fundamental mode CO_2 laser coupled to an operating microscope with a 400-mm objective lens. After exposure of one arytenoid cartilage, the posterior commissure, and half of the other arytenoid, the mucoperichondrium overlying the accessory corniculate cartilage and the apex of the arytenoid was vaporized to expose the underlying cartilage (see Figure, B). The laser was set in the repeat, intermittent mode (0.1 second) at 1,990 W/cm^2 with a focused spot size of 0.8 mm. The focused spot size of 0.8 mm was used throughout the procedure. The corniculate cartilage and apex of the arytenoid cartilage were vaporized with use of the laser in the continuous mode with the same power density as the preceding step (see Figure, C). Next, the mucoperichondrium overlying the upper body of the arytenoid cartilage was ablated by switching the laser back to the repeat, intermittent mode (0.1 second) at 1,990 W/cm^2 (see Figure, D). With the laser in the continuous mode at 3,185 W/cm^2, the upper body of the arytenoid cartilage was vaporized (see Figure, E). At this time, the laser was switched back to the repeat, intermittent mode (0.1 second) at 1,990 W/cm^2, and the mucoperichondrium overlying the lower body of the arytenoid was ablated to expose the underlying cartilage (see Figure, F). The lower body of the arytenoid was now ablated by working from lateral to medial with the laser still set to the repeat, intermittent mode (0.1 second) at 1,990 W/cm^2. The lateral ligament was encountered and cut during this step, and the arytenoid was vaporized laterally down to the underlying cricoid cartilage, while medially, the muscular and vocal processes remained (see Figure, G). Next, the mucoperichondrium overlying the vocal process and most of the muscular process was ablated, still



Procedure. A) Endoscopic view of larynx with bilateral vocal cord paralysis in paramedian position. B) View of larynx after mucoperichondrium overlying corniculate cartilage and apex of arytenoid cartilage have been ablated. C) Corniculate cartilage and apex of arytenoid cartilage have been ablated, exposing apex of arytenoid. D) Mucoperichondrium overlying upper body of arytenoid cartilage has been vaporized. E) Upper body of arytenoid cartilage has been ablated. F) Mucoperichondrium overlying lower body of arytenoid cartilage has been vaporized. G) Arytenoid has been ablated down to underlying cricoid cartilage laterally, while medially vocal and muscular processes remain. H) Mucoperichondrium overlying vocal process has been vaporized, exposing vocal process and vocalis muscle. I) Vocal process and muscular process have been ablated. Anterior-medial to posterior-lateral area of vocalis muscle has been vaporized 2 to 3 mm anterior to vocal process to create posterior triangulation to airway. Note area of ablation lateral to vocalis muscle (arrow) to facilitate lateralization of vocal cord. J) Final postoperative result of operation. Wound is covered with healthy-appearing mucosa by end of third postoperative week.

RESULTS OF EACH SERIES

	Postoperative Airway		Lost to Follow-up	Total No. of Cases
	Adequate	Inadequate		
First series	10	1	0	11
Long-term follow-up of first series	7	1	2	10
Second series	17	0	0	17
Combined series	24	2	2	28

with the laser in the repeat, intermittent mode (0.1 second) at 1,990 W/cm^2 (see Figure, H). At this time, the vocal process with an adjacent portion of the vocalis muscle and the muscular process up to but not including the attachment of the interarytenoideus muscle was vaporized. The mucosal cut began 2 to 3 mm in front of the vocal process and was beveled anterior-medial to posterior-lateral to create a triangulated posterior airway. During this step, great care was exercised not to encroach upon or vaporize the mucosa of the interarytenoid cleft. Next, a small area lateral to the vocalis muscle was vaporized to facilitate lateralization of the vocal cord during healing (see Figure, I). Further lateralization of the vocal cord occurred during healing. The wound was covered by a white coagulum from the second postoperative day through the second or third postoperative week. By the end of the third postoperative week, the wound was covered by healthy-appearing mucosa (see Figure, J).

All of the patients in the combined series were covered by a broad-spectrum antibiotic (cefazolin sodium) for 5 postoperative days. Additionally, an intraoperative dose of dexamethasone sodium phosphate (10 mg) was given to all patients in this series.

RESULTS

First Series. Ten of 11 patients in this series had successful restoration of their airways and were decannulated at the time of the original presentation in 1984 (see Table). One patient developed a posterior laryngeal web and was discharged with an indwelling tracheotomy; she refused further surgical intervention. Follow-up on that group of patients revealed that 7 of the 10 successfully treated patients remain decannulated with a good airway, although 2 of these 7 patients required a revision procedure to excise a granuloma. Two of the 10 patients were lost to follow-up, and 1 patient experienced symptoms of respiratory distress at 15 months postarytenoidectomy and required a tracheotomy for airway management (see Table). This patient has failed two subsequent revision procedures and remains with a tracheotomy at this time. The follow-up period on these patients ranged from 6½ years to 9 years.

Second Series. All 17 patients in this series had successful restoration of their airway; the 16 of these patients with indwelling tracheotomies were decannulated within 2 months of the arytenoidectomy procedure (see Table). The patient on whom the endoscopic laser arytenoidectomy was performed without a tracheotomy experienced moderate postoperative edema that responded favorably to intravenous corticosteroids (dexamethasone sodium phosphate, 10 mg). The follow-up period on these patients ranged from 3½ years to 5½ years.

Combined Series. When the first and second series are combined, a total of 28 patients with bilateral vocal cord paralysis were operated upon by eight different otolaryngologist–head and neck surgeons using the same endoscopic laser arytenoidectomy technique. Twenty-four of the 28 patients (86%) were successfully managed in the combined series; 2 patients (7%) were lost to follow-up, and 2 patients (7%) failed treatment (see Table). The overall follow-up period of the combined series was 3½ years to 9 years.

DISCUSSION

In 1984, Ossoff et al[1] wrote that the use of the CO2 laser for the treatment of patients with bilateral vocal cord paralysis was "a logical extension of the clinical application of this instrument." The results of this retrospective review of 28 patients with bilateral vocal cord paralysis who have been operated upon by eight different otolaryngologist–head and neck surgeons, all using the same endoscopic laser arytenoidectomy technique, serve to validate this statement. Use of the CO2 laser attached to the operating microscope affords the otolaryngologist–head and neck surgeon the opportunity to perform precise, hands-off, endoscopic operations through the relatively narrow operative field of the microlaryngoscope. Precision, hemostasis of the microcirculation, and decreased intraoperative edema are the advantages associated with the use of the CO2 laser in this operation; these characteristic attributes of this laser help to facilitate visualization and control over the final result of the operation. The authors' prior experience with the Thornell endoscopic arytenoidectomy procedure was associated with poor visualization, intraoperative edema, and frequent, troublesome bleeding. All three of these limitations added to the technical difficulties of performing an endoscopic arytenoidectomy. The development of the surgical technique outlined step by step in this paper in combination with the use of the CO2 laser has helped to solve a difficult clinical problem for the authors. Ablation rather than excision and delivery of the arytenoid cartilage represents the major difference between this operation and the traditional Thornell endoscopic arytenoidectomy.

Disadvantages associated with this surgical technique include 1) less control in the placement of the vocal cord than obtained with external operations and 2) a learning curve on a relatively new surgical delivery system. Associated with this latter disadvantage is the possibility of experiencing direct or reflected laser irradiation if the beam should inadvertently be reflected off an instrument or the proximal rim or lumen of the microlaryngoscope. Most CO_2 laser microscope adapters have an inherent parallax error incorporated into their design by having the laser beam be reflected off a gimballed mirror assembly that does not allow for absolute parallelism with the optical plane of the laryngoscope lumen. This design causes difficulty in working in the posterior commissure of the larynx and often requires the surgeon to overangulate the microscope. Many of the newer microscope adapters and microspot adapters are designed to overcome this problem by incorporating the use of a dichroic mirror assembly that allows for parallel passage of the beam through the optical lumen of the laryngoscope. This improvement has been made possible through advances in laser optics design and coatings. Potential complications include the formation of a granuloma, formulation of a posterior glottic web, failure to gain an adequate postoperative airway, loss of adequate voice production, cricoid perichondritis, and the risk of an endotracheal or tracheotomy tube ignition causing an airway explosion or burn.

Granuloma formation most probably occurs secondary to retained carbonaceous debris from the laser operation, although gastroesophageal reflux is another possible cause. Both of our patients who acquired granulomas in their postoperative course were placed on a 1-month course of histamine H_2 receptor antagonists at the time that their granuloma was excised.

The postoperative complication of a posterior glottic web associated with failure to gain an adequate airway experienced by the fourth patient in our first series most likely resulted from a submucosal thermal injury to the heat-sensitive tissue of the posterior commissure and interarytenoid cleft. This anatomic area is quite vulnerable during endoscopic laser arytenoidectomy and must be protected from any direct or indirect submucosal laser irradiation to prevent the formation of a posterior glottic web or fibrosis, both of which can lead to further compromise of an already compromised airway. The occurrence of posterior glottic scarring and airway compromise requiring repeat tracheotomy at 15 months postoperatively in one of our patients most probably represents another example of submucosal thermal injury in the heat-sensitive posterior commissure. This delayed cicatricial response, in contrast to the more immediate response in the other patient, may have occurred because of a less severe, but still significant, intraoperative submucosal thermal injury.

Loss of adequate voice production did not occur in our series; instead, our patients experienced only a small amount of voice loss. The minimal voice loss associated with this operation results from the surgeon's ability to accurately open the posterior laryngeal lumen to create an airway while leaving the anterior half of the operated vocal cord untouched and in close apposition to the contralateral, unoperated vocal cord. Because the operated cord is not lateralized, this close apposition of the two cords facilitates phonation with a postoperative voice that we have subjectively characterized as being high-average to good; however, when we compare the results to those of other arytenoidectomy procedures, both endoscopic and extralaryngeal, we reclassify the voice as being very good.

Cricoid perichondritis is a theoretic complication that we have not encountered in our experience; because the cricoid cartilage is exposed during this operation, we have included it for completeness.

Endotracheal or tracheotomy tube ignition is a potential catastrophic complication of laser operations in the upper aerodigestive tract that can be readily avoided by following the appropriate safety precautions. Plastic tracheotomy tubes should not be used, but rather metal tracheotomy tubes, red rubber or silicone endotracheal tubes wrapped with reflective metallic tape, or special endotracheal tubes manufactured for use with the CO_2 laser. When a cuffed tube is used, the cuff should be inflated with methylene blue–colored saline and further protected by use of saline-saturated neurosurgical sponges and the operating platform between the cuff and the vocal cords. Sponges should not be used when a cuff is not present on the tracheotomy or endotracheal tube. Oxygen should not exceed 40% in the anesthetic gas mixture and should be diluted with helium, nitrogen, or room air. Of these three gases, helium represents the safest choice because of its heat-quenching properties. Nitrous oxide, like oxygen, is a potent oxidizing gas and should not be used to dilute the oxygen concentration.[35,36]

Appropriate application of laser energy to the operative field is associated with decreased scarring and predictable wound healing. Deviation from the suggested laser paradigms discussed in Materials and Methods is not recommended. Application of too much laser energy per unit time can cause excessive scarring of the target tissues; therefore, it is of the utmost importance to use the intermittent mode during all parts of this operation except for the vaporization of the upper body of the arytenoid cartilage. With the exception of this step in this operation, the authors do not recommend use of the continuous mode.

The power densities presented in this paper were calculated from the laser manufacturer's specification sheet and do not represent actual measured power densities at the operative site. Regardless, they should serve as an excellent starting point with respect to performing this procedure. It is entirely possible that these parameters will need to be adjusted frequently during the procedure should the actual clinical conditions change.

Although one patient in our series was operated on without an indwelling tracheotomy, we do not recommend performing this surgical procedure in the absence of a tracheotomy. In the Thornell technique, the tracheotomy is performed in a staged fashion preceding the endoscopic arytenoidectomy by several weeks; but we have performed the tracheotomy immediately prior to the endoscopic laser arytenoidectomy without experiencing any difficulty.

CONCLUSIONS

This paper is a retrospective analysis of 28 patients managed by eight different surgeons using the same operative technique to perform the endoscopic laser arytenoidectomy procedure. Twenty-four of the 28 patients (86%) were successfully managed in this combined series; 2 patients (7%) were lost to follow-up and 2 patients (7%) failed treatment. The overall follow-up period of these patients was 3½ years to 9 years.

From the results of this study it can be concluded that endoscopic laser arytenoidectomy is a reliable treatment option for the management of patients with bilateral vocal cord paralysis. Furthermore, this retrospective analysis proves that the technique and results are reproducible and withstand the test of time.

ACKNOWLEDGMENTS — The authors thank Herbert I. Moselle, MD, Philip E. Andrews, MD, and Willis G. McMillan, MD, for their generosity and kindness in helping us to include follow-up data on their cases, presented in the 1984 paper,[1] in this manuscript.

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LARYNGEAL FRAMEWORK RECONSTRUCTION WITH MINIPLATES

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SYRACUSE, NEW YORK

Defects of the laryngeal framework after trauma, cancer, and thyroplasty have been reconstructed with mini-reconstruction plates. Six patients had miniplates used to repair the thyroid cartilage defect after type I thyroplasty to prevent lateralization of the Silastic implant; three patients had miniplates used after hemilaryngectomy to bridge the thyroid cartilage remnants, resulting in better deglutition after hemilaryngectomy; and three patients had miniplates used to repair laryngeal fractures. The plates were tolerated well by the patients; there were no major complications. Rigid fixation using miniplates for laryngeal reconstruction has unique advantages over the use of wires. It offers the advantages of rigid and immediate stabilization with the ability to bridge large defects. It can be an alternative to existing techniques of laryngeal reconstruction.

KEY WORDS — laryngeal framework reconstruction, miniplates.

INTRODUCTION

Rehabilitation of the larynx after trauma, cancer, and irradiation remains a perplexing and challenging problem. A key element in achieving satisfactory results is restoration of the laryngeal skeletal framework. The larynx is a relatively small structure. Its anatomy and tissue characteristics make immobilization of the larynx difficult. Stabilization and promotion of primary healing in this area is often not possible.[1] These challenging problems have prompted many surgeons to develop a variety of ingenious techniques for reconstruction of the larynx. Soft tissue, locally transposed cartilage, and autogenous grafts have all been used. Artificial materials such as Teflon, Silastic, and hydroxylapatite have also been tried with success.[2-10]

Historically, laryngeal framework repair utilizes sutures to approximate mucosal and soft tissue defects, while wires are used to maintain cartilage contact. Although good results have been reported, late glottic insufficiency, aspiration, and laryngeal stenosis continue to be problems encountered after laryngeal reconstruction.[11-13]

Recently, mini-reconstruction plates have been used with success in reconstruction of the facial skeleton.[14-16] These miniplates have certain advantages over wires. They are designed to be bent and fixed into place with screws. Once fixed in position, they maintain rigid fixation in all three dimensions. Plating fixation has been used after fractures and osteotomies in the midfacial area to bridge large defects as well as to maintain rigid stabilization of bone grafts. By use of these miniplates in reconstructing the larynx, the advantages of immediate and rigid stabilization may be applied to laryngeal framework surgery.

This paper describes mini-reconstruction plates used for reconstruction of thyroid cartilage defects. Rigid fixation and laryngeal framework stabilization can be applied to reconstructive problems encountered after vertical hemilaryngectomy, after thyroplasty for vocal fold medialization, and after laryngeal cartilage fracture.

MATERIAL AND METHODS

From 1988 to 1990, 12 mini-reconstruction plates were applied to the thyroid cartilage in 12 patients. Plates were used to 1) stabilize the segments of thyroid cartilages after laryngeal fracture to restore the proper geometry (three cases), 2) bridge large defects of the thyroid cartilage after vertical hemilaryngectomy (three cases), and 3) bridge thyroid cartilage defects after Isshiki type I thyroplasty for vocal fold medialization (six cases). The rationale and exact procedure for use of the plates depend upon the type of operation performed and the resultant laryngeal framework defect. These considerations will be described briefly below.

Laryngeal Fracture. When traumatic injury results in laryngeal fracture with displacement, restoration of the proper thyroid cartilage angle is difficult to achieve with wires and stents. Reconstruction plates can be used instead to restore proper geometry of the thyroid cartilage. By bending the miniplate to the desired configuration and then fixing the fractured laryngeal fragments to the plate with screws, the laryngeal fracture can be reduced precisely, immediately, and with rigid stability. The principles and surgical techniques of laryngeal fracture repair are similar to those of open reduction and interosseous fixation in the facial skeleton. Instead of wires, mini-reconstruction plates are used.

At surgical exploration, if there is no mucosal disruption, reduction of the laryngeal fracture with plates is the only repair used. If there is extensive in-

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Presented at the meeting of the American Laryngological Association, Palm Beach, Florida, April 28-29, 1990.

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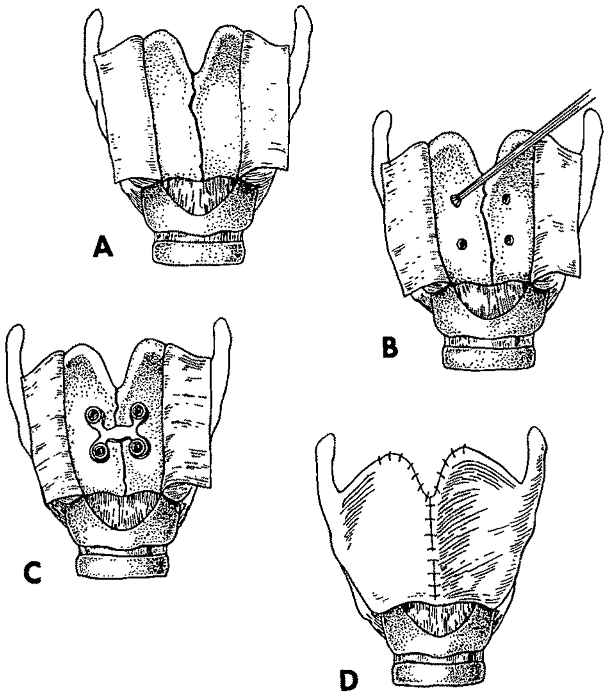


Fig 1. Laryngeal fracture repair. A) Laryngeal fracture is explored after elevation of perichondrial flaps. B) 1.0-mm otologic bur is used to drill holes in thyroid cartilage. C) H-shaped miniplate, bent to normal thyroid cartilage angle, is applied and screwed into place. D) Perichondrium is closed.

jury to the mucosa, standard laryngeal stents are used. Figure 1 diagrams the use of plates to repair a midline fracture of the thyroid cartilage.

Reconstruction After Vertical Hemilaryngectomy. When there is tumor invasion of the anterior commissure, resection of the involved thyroid cartilage and part of the contralateral thyroid cartilage is necessary. After vertical hemilaryngectomy done in the manner described by Bailey[17] and by Biller et al,[18] the miniplate is bent and applied to maintain the proper position and alignment of the remaining thyroid cartilage segments. The reconstruction plate is placed over the bipedicled perichondrial muscle flap and then the sternohyoid muscle is closed over the plate. This configuration serves two purposes. First, it maintains the position of the remaining thyroid cartilage and prevents medialization of the thyroid cartilage remnant. Second, the plate prevents any lateral migration of the bipedicled perichondrial flap. This application is diagramed schematically in Fig 2.

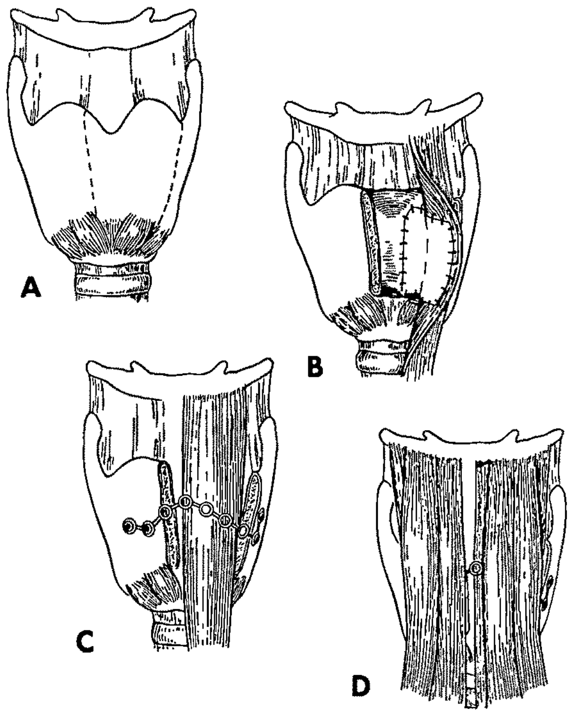


Fig 2. Reconstruction after vertical hemilaryngectomy. A) Outline of cartilage cuts and hemilaryngectomy defect. B) Bipedicled perichondrial muscle flap sutured into position to mucosa. C) Rigid stabilization of thyroid cartilage remnant with reconstruction plate. D) Closure of sternohyoid muscle over plate.

Thyroplasty. After thyroplasty for vocal fold medialization, the thyroplasty window defect is bridged with a reconstruction plate. The rationale for plating is to provide for better repair of the thyroid cartilage after thyroplasty. The miniplate serves to prevent lateral migration of the Silastic implant. Furthermore, if additional vocal fold medialization is needed, small pieces of Silastic can be wedged between the existing implant and the plate, thereby avoiding the carving of a new implant. Figure 3 illustrates the steps in cartilage reconstruction and Silastic implant placement.

Technique of Plating. The mini-reconstruction plates are stainless steel plates made to be bent in three dimensions (Arbeitsgemeinschaft für Osteosynthesefragen–Association for the Study of Internal Fixation[14]). The plates are used to bridge defects and stabilize fragments of bone in the desired position by the use of screws. The plates accept either 1.5- or 2.0-mm screws. The technical aspects of miniplate application are similar to those of fracture repair in the facial skeleton and will not be discussed in depth here. Some modifications of the technique are necessary to adapt the plates for laryngeal framework surgery.

Care must be taken not to injure the laryngeal muscles deep to the thyroid cartilage. To this end, a diamond 1.0-mm otologic bur can be used instead of the 1.1-mm dental drill. This bur decreases the risks of inner perichondrial tear. The screws are then fixed to the plate and to the cartilage without tapping. During screw placement, the most critical step is to fasten the screw and plate into position without "stripping" the cartilage. Tactile feedback guides the surgeon as to the end point of screw fixation. In comparison to facial bone fixation, there is much less increase in resistance as the screws tighten on cartilage and reach their end point. If the hole to receive the screw becomes "stripped," it is best to use another hole on the mini-reconstruction plate.

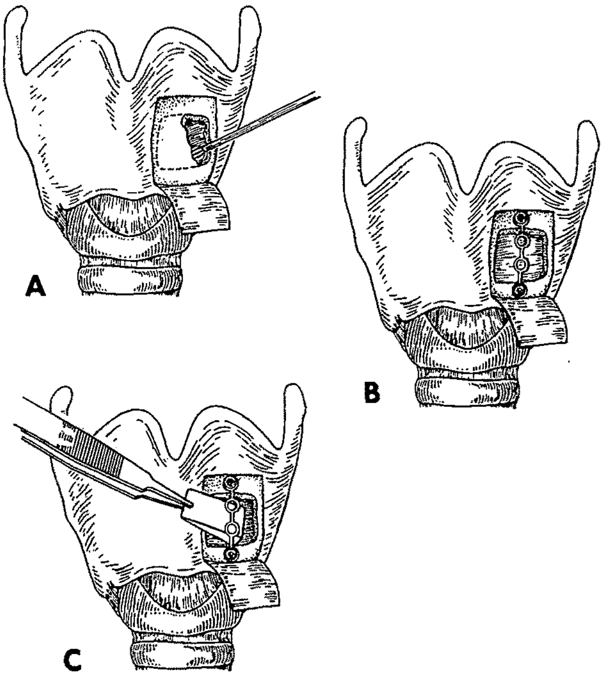


Fig 3. Reconstruction after thyroplasty. A) Creation of thyroplasty window. B) Application of miniplate after initial implant has been placed. C) Additional implant being wedged into position to achieve extra medialization.

Alternatively, the larger 2.0-mm screw can be used. The lengths of the screws we used were either 4 or 6 mm. The choice depends on the thickness of the thyroid cartilage as measured by the depth gauge. For thyroplasty window defects, a single screw on each side of the defect serves to fixate the plates in position. For cases in which there is complete separation of laryngeal segments, use of two screws on each fragment is desirable. The holes were all drilled centrally and no attempt was made to compress the fragments.

RESULTS

The total time since operation varies from 4 months to 24 months (see Table). The total time with plates in place is greater than 100 patient months. These plates were well tolerated without marked side effects. There were no instances of perioperative or postoperative infection. There has been no extrusion of plates or screws. The plates used in thyroplasty candidates were applied under local anesthesia without compromise to the airway. Examination of the endolarynx after thyroplasty showed petechiae and mucosal edema similar to that seen after standard thyroplasty. The thyroplasty patients all showed improved function. One patient complained of some mild increase in difficulty with solid foods. This patient had a prior Zenker's diverticulum resection. Postoperatively, thyroplasty patients have maintained voices comparable to those achieved during operation. There was no significant deterioration of the postoperative voice quality compared to intraoperative results. The patients' voices, although far from normal, improved in quality, loudness, and breathiness. The radiographic appearance after operation in one patient is shown in Fig 4.

There were two patients with laryngeal fractures that were repaired immediately with plates. These two patients have since been decannulated with good voice and swallowing function. A computed tomography scan on the patient in case 10 shows a widening of the thyroid cartilage angle due to trauma (Fig 5A). Postoperative computed tomography on the same patient showed restoration of a more normal thyroid cartilage position being maintained with the miniplate (Fig 5B). The third patient with a laryngeal fracture had a delay in her laryngeal fracture diagnosis and repair; she required further soft tissue repair for laryngeal stenosis after her initial operation. The plate was removed electively during a subsequent operation.

As a group, the hemilaryngectomy patients did surprisingly well after operation and plate reconstruction. All were successfully decannulated on postoperative day 8. Their airway and deglutition function after plating reconstruction seemed better than those after standard hemilaryngectomy. Included in this group is a patient who had resection of both membranous true vocal cords and extensive anterior cartilage loss. Figure 6 documents a barium swallow study done on the seventh postoperative day. Although mild aspiration is seen, his swal-

CASES OF LARYNGEAL FRAMEWORK RECONSTRUCTION WITH MINIPLATES

Case	*Age (y)*	*Sex*	*Diagnosis*	*Operation*	*Plate Size (No. of Holes)*	*No. of Screws*	*In Situ Time (mo)*
1	62	M	Vocal cord paralysis	Thyroplasty	4	2	6
2	41	F	Vocal cord paralysis	Thyroplasty	3	2	10
3	59	F	Vocal cord paralysis	Thyroplasty	4	2	9
4	69	M	Glottic insufficiency	Thyroplasty	5	4	13
5	33	M	Vocal cord paralysis	Thyroplasty	4	2	7
6	82	M	Vocal cord paralysis	Thyroplasty	3	2	10
7	58	F	Glottic carcinoma (T2)	Hemilaryngectomy	8	4	24
8	59	M	Glottic carcinoma (T2)	Hemilaryngectomy	9	4	18
9	62	M	Glottic carcinoma (T2)	Hemilaryngectomy	8	4	18
10	72	M	Laryngeal fracture (acute)	Fracture repair	4	4	18
11	68	M	Laryngeal fracture (acute)	Fracture repair	4	4	9
12	21	F	Laryngeal fracture/stenosis (late)	Fracture repair	3	4	1

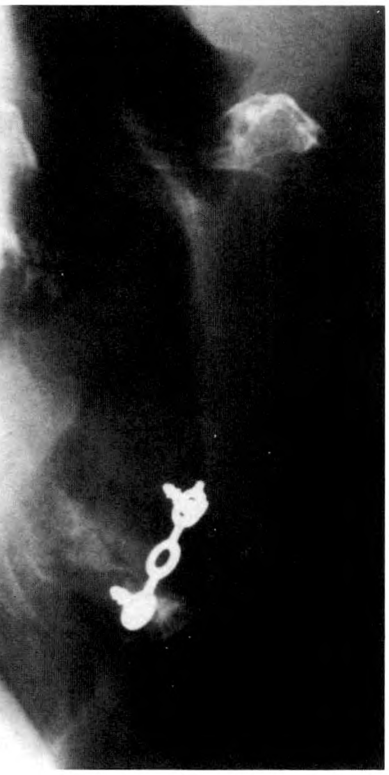


Fig 4. (Case 6) Lateral radiographic appearance of neck after thyroplasty.

lowing function after operation was surprisingly good. Fiberoptic endoscopic examination after operation in these patients showed a rapid return of the ability to clear the pharynx of secretions. By day 5, the pooling within the pyriform sinus was minimal. A barium swallow study on the seventh day after operation showed minimal to no aspiration. Because of the early return of swallowing function, these patients' hospital stays were shorter. The average hospitalization time for the patients undergoing thyroplasty was 1 day. The hospitalization time for hemilaryngectomy was 8 days. The hospitalization time for laryngeal fracture was longer because of other injuries unrelated to laryngeal fracture.

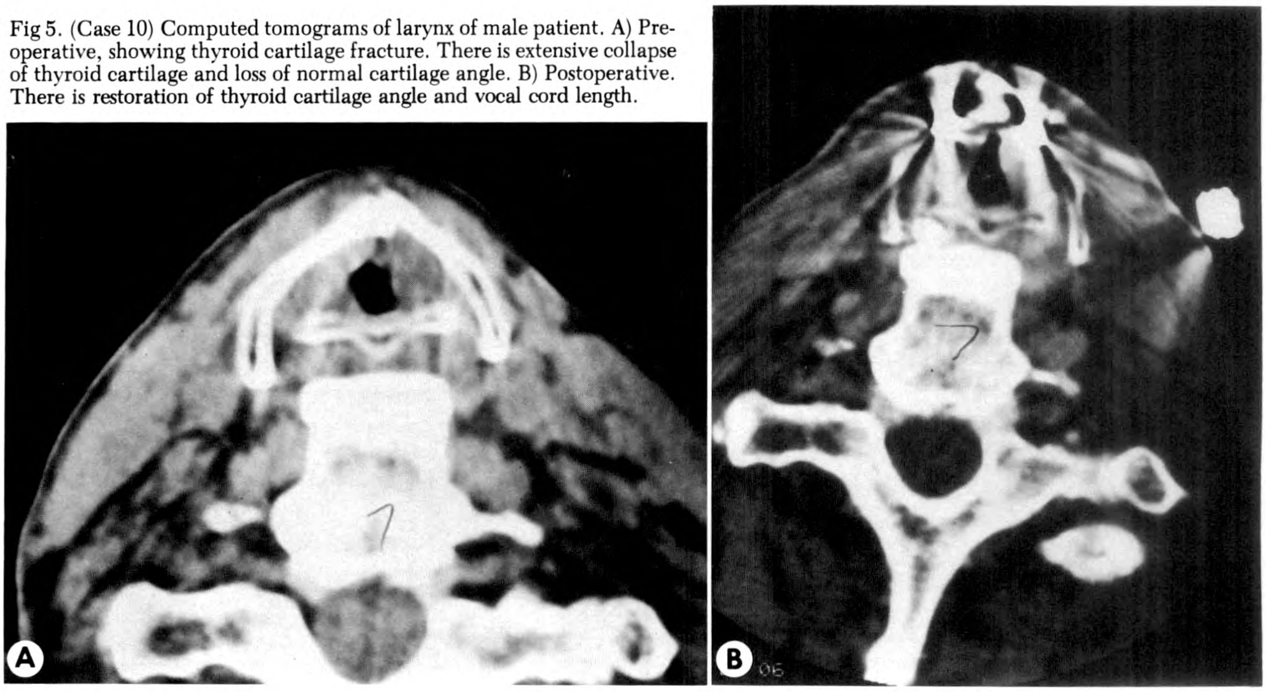
All but one of the laryngeal plates are still in situ. One thyroplasty patient died of lung carcinoma 10 months after plating. Two patients have undergone laryngoscopy for cancer biopsy with negative biopsy results. One patient with chronic laryngeal stenosis had the plate electively removed at a subsequent operation. At the time of removal, the plate was in good position.

DISCUSSION

Rigid fixation of the laryngeal skeleton may be a good adjunctive technique in reconstruction of thyroid cartilage defects. The unique advantages of plating fixation over more traditional use of wires are attributable to the combined advantages of immediate restoration of rigid stability and the ability to bridge large defects. These miniplates are bendable in three dimensions and conform nicely to the complex geometry of the area. Immediate restoration of rigid stability has advantages in laryngeal reconstruction. First, rigid fixation allows fracture repair with primary healing. There is less likelihood of rotation and movement of the laryngeal fragments when rigid stabilization can be established. Second, by use of rigid miniplates, the dimensions of the laryngeal airway can be maintained with less fear of cartilage absorption, necrosis, chondritis, or stenosis.

Fixation of the laryngeal fragments after hemi-

Fig 5. (Case 10) Computed tomograms of larynx of male patient. A) Preoperative, showing thyroid cartilage fracture. There is extensive collapse of thyroid cartilage and loss of normal cartilage angle. B) Postoperative. There is restoration of thyroid cartilage angle and vocal cord length.



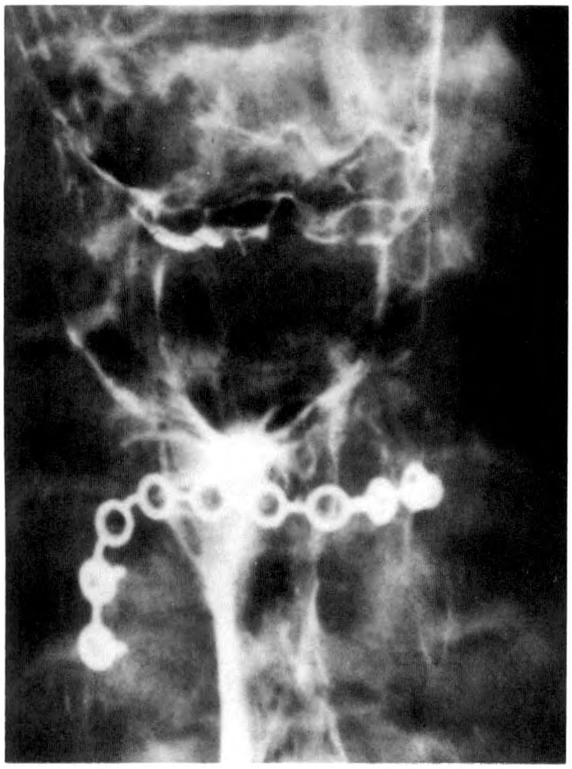


Fig 6. (Case 8) Barium swallow study 7 days after hemilaryngectomy reconstruction. Patient had bilateral vocal cord excision with small posterior thyroid cartilage remnant. Note good clearance of pharynx, symmetry of pyriform sinus, and minimal aspiration.

laryngectomy solves a difficult problem in laryngeal reconstruction. Although nasal septal grafts and local cartilage rotation can be used, immediate and rigid fixation of the laryngeal segments is difficult to achieve with wires. The use of reconstruction plates allows the laryngeal framework to be immediately stabilized. This permits the inferior constrictor muscle to contract normally against a stabilized laryngeal cartilage, thereby improving deglutition after hemilaryngectomy. This improved deglutition is supported by endoscopic observations of the larynx and pharynx after operation. In patients with plating fixation, there has been less pooling of saliva in the hypopharynx. Pharyngeal swallowing and mucus clearance occur with less effort than after standard hemilaryngectomy.

In thyroplasty, restoration of the thyroplasty window by the miniplate allows the Silastic laryngeal implant to be placed with less risk of lateralization. Solid lateral support of the implant helps the paralyzed larynx to withstand forces exerted from the contralateral vocal cord during coughing and speaking. With the miniplate placed over the thyroplasty window, the position of the implant is not as dependent on careful placement of the Silastic block within the thyroplasty window. With the added lateral support, fine adjustment of vocal fold medialization can be accomplished by wedging smaller pieces of implant into desired areas of the larynx. The possibility of migration of the implant laterally during the postoperative period is diminished.

In laryngeal fracture repair, the use of screws and plates obviates the need to pass wires through the larynx. Immediate fixation restores a stable platform upon which the normal laryngeal skeleton can be restored.

The disadvantages of plates are their costs, the added time to the operation, and the added skill that needs to be developed by the surgeon. The plates and screws used are small. When they are used on cartilage, overvigorous application of the screw will result in "stripping" of the screw site. Because the plates are rigid, it is not a forgiving technique if the fragments are misaligned. On the other hand, the added time needed to bend and apply the plates is compensated for by the lack of extensive suturing and wiring.

An untested area of plating reconstruction is the ability of the plates to tolerate postoperative irradiation. The possibility of radiation scatter resulting in radiation-induced chondritis has not yet been excluded. Because the plates are metallic, they do interfere with subsequent computed tomography and radiographic imaging. Their biocompatibility has not been tested in the magnetic resonance imaging scanner.

Despite the potential problems of long-term extrusion, the miniplates are inert implants placed on a non–weight-bearing framework, and on the basis of experiences with midface fractures, they have been left in situ. At the present time, cautious optimism regarding the use of these plates for laryngeal reconstruction seems warranted. Their application in laryngeal reconstruction can be justified if more traditional techniques fail to achieve similar results.

Although many questions with laryngeal plating reconstruction remain to be answered, this study has demonstrated the following.

1. Principles of internal rigid fixation can be applied to the laryngeal skeleton.
2. Plates are well tolerated in situ.
3. Insertion of plates is associated with little increase in operating time or morbidity.
4. In certain situations in which wires fail to achieve the desired stabilization, plates offer unique advantages. Their usage in hemilaryngectomy reconstruction, in thyroplasty, and in laryngeal fracture repair has reduced hospitalization time while improving functional results.

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INTERNATIONAL HEARING AID CONFERENCE: SIGNAL PROCESSING, FITTING, & EFFICACY

The International Hearing Aid Conference: Signal Processing, Fitting, & Efficacy will be held June 21-23, 1991, at The University of Iowa, Iowa City, Iowa. The organizing committee includes Richard S. Tyler, PhD (Signal Processing), Chaslav V. Pavlovic, PhD (Fitting), and Ruth A. Bentler, PhD (Efficacy). Further information may be obtained from any member of the organizing committee at the Department of Speech Pathology and Audiology, The University of Iowa, Iowa City, IA 52242; (319) 335-8726, FAX (319) 335-8851.

Ann Otol Rhinol Laryngol 99:1990

COMBINED LARYNGEAL FRAMEWORK MEDIALIZATION AND REINNERVATION FOR UNILATERAL VOCAL FOLD PARALYSIS

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The laryngeal framework–Silastic implant technique has become an increasingly attractive alternative to Teflon injection, particularly when there is fixation of the cricoarytenoid joint or the defect to be corrected is larger than usual; but it does not restore ability to change tension in the vocal fold. Unilateral vocal fold reinnervation can overcome this drawback and, when used in conjunction with surgical medialization, may offer return of function very close to normal. Twenty-nine patients with unrecovered unilateral vocal fold paralysis and/or fixation of the cricoarytenoid joint have been managed by use of a Silastic implant combined with unilateral vocal fold reinnervation with no complications. Voice improvement has been assessed on preoperative and postoperative voice recordings. The combined surgical techniques for reinnervation and a modification of Silastic implantation via the laryngeal framework approach are reported.

KEY WORDS — laryngeal framework surgery, Silastic implant, vocal fold reinnervation.

For many otolaryngologists Teflon injection remains the procedure of choice for unrecovered and poorly compensated unilateral vocal fold paralysis. Because voice improvement after Teflon injection is less reliable 1) when there is fixation of the cricoarytenoid joint, 2) when combined superior and recurrent laryngeal nerve paralyses result in large gaps at the posterior commissure, and 3) because Teflon can be removed only with difficulty,[1] interest in surgical medialization via the laryngeal framework surgery approach has been increasing.[2-4] Although this is an open surgical procedure, it can be carried out under local anesthesia, does not require routine overnight stay, and has provided very satisfactory voice results with a low incidence of complications. The other advantages of this approach are outlined in the Table.

Although excellent vocal fold medialization with improved loudness and sustainability of voice may be achieved by either Teflon injection or a Silastic implant, unrestored motor innervation may yet be responsible for diplophonia and poor voice quality, since neither of these techniques can restore tonus, muscle turgor, or ability to tense the vocal fold. The only technique now available that can restore these functions is reinnervation,[5,6] which has succeeded as the sole means of rehabilitation for unilateral vocal fold paralysis, but which imposes a delay of up to 6 months between the operation and beginning return of function. Since the surgical approach for nerve-muscle pedicle reinnervation is virtually identical to that for medialization by a Silastic implant, a combination of the two procedures was undertaken in hopes of providing a prompt increase in loudness secondary to the implant and later improvement in vocal quality and pitch control due to the reinnervation.

MATERIALS AND METHODS

Twenty-nine candidates were selected from among 70 consecutive patients with unilateral vocal fold immobility seen in the author's practice between January 1, 1987, and December 31, 1989. Each was judged to be a less than optimal candidate for Teflon injection because of fixation of the cricoarytenoid joint, combined superior and recurrent laryngeal nerve paralyses, and/or severe wasting of vocal fold musculature. Preoperative and postoperative voice recordings were obtained in all cases, and videostroboscopy in the more recent ones. The relative advantages and disadvantages of the various approaches to rehabilitation of voice were discussed and the patients each volunteered to undergo combined Silastic implant medialization and reinnervation.

All operations were carried out under combined topical and local infiltration anesthesia. Pontocaine 0.5% was sprayed between the vocal folds to diminish coughing and swallowing, and Xylocaine 1% with epinephrine 1:100,000 was injected into the skin and perilaryngeal tissues on the side of paralysis to achieve surgical anesthesia. Only a few of the patients required intravenous sedation with Valium or Versed during the procedure.

After sterile skin preparation and draping, a skin

COMPARISON OF LARYNGEAL FRAMEWORK SURGERY AND TEFLON INJECTION

Laryngeal Framework Surgery With Silastic Implant	*Teflon Injection of Vocal Folds*
Outpatient procedure	Outpatient procedure
Local anesthesia	Topical anesthesia
Any size defect	2- to 4-mm defect
Can medialize fixed arytenoid	Cannot medialize fixed arytenoid
Easily removed	Removed with difficulty
Can reinnervate	Cannot reinnervate

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Presented at the meeting of the American Laryngological Association, Palm Beach, Florida, April 28-29, 1990.

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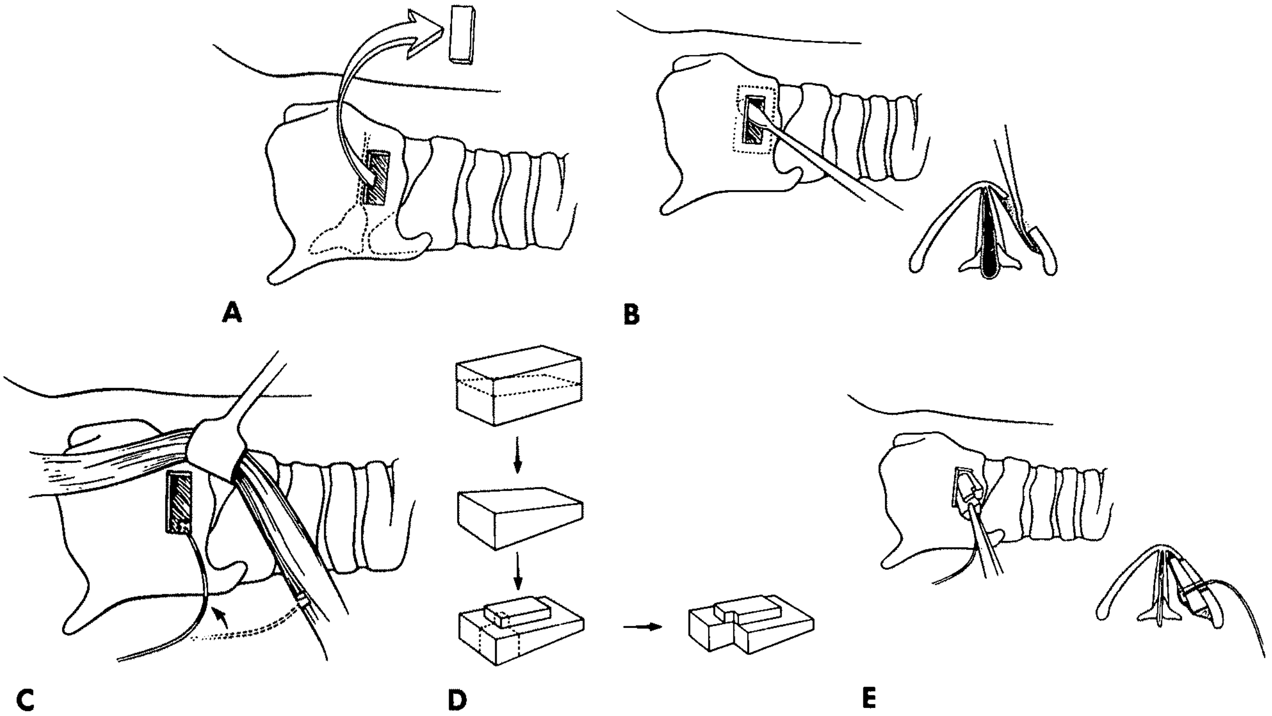

Procedure. A) Cartilage window is removed for access to lateral thyroarytenoid muscle and as template for Silastic block. B) Pocket is dissected between inner surface of thyroid cartilage and perichondrium. C) Previously prepared nerve-muscle pedicle is sutured to outer surface of lateral thyroarytenoid muscle. D) Wedge-shaped implant is carved from block of Silastic, with cartilage window used as template. E) Implant is placed into pocket with corner removed to accommodate nerve-muscle pedicle and medialize vocal fold.

crease incision was made at the level of the lower border of the thyroid cartilage, beginning at the midline and extending posteriorly to just behind the anterior border of the sternocleidomastoid muscle. This incision was carried through skin, superficial fascia, and platysma muscle, permitting the development of flaps in the subplatysmal plane. The sternocleidomastoid muscle was mobilized posteriorly and the jugular vein identified. A nerve-muscle pedicle was developed, most often from the branch of the ansa hypoglossi to the anterior belly of the omohyoid muscle, although other strap muscle branches were used on occasion.[5] A nerve stimulator was used to help identify the nerve, which responded to electrical stimulation at 1 to 1.5 mA in spite of the use of local anesthetic.

The pedicle was laid aside and the lateral aspect of the thyroid cartilage was exposed by retraction of the overlying strap muscles. A scalpel incision or saw cut was made (depending upon the degree of calcification of the thyroid ala) parallel to the vocal fold and judged to be at or slightly below its upper surface. Most often this level was at the midpoint between the thyroid notch and the lower border of the thyroid cartilage when measured at the midline. Additional cuts were made at right angles to describe an oblong window in the lower half of the thyroid ala, with care taken to leave intact cartilage struts of 3 or 4 mm anteriorly, inferiorly, and posteriorly (see Figure, A). The cartilage window was removed intact by dissecting it free from its underlying inner perichondrium and the thyroarytenoid muscle. The inner perichondrium was further dissected in all directions from the edges of the window to create a generous pocket (see Figure, B). Posterior dissection permitted mobilization of the arytenoid cartilage toward the midline if it was ankylosed. The inner perichondrium was removed from the area of the window to expose the underlying muscle, and the previously prepared nerve-muscle pedicle was sutured to the surface with two stitches of 5-0 monofilament nylon (see Figure, C). A block of Silastic was carved to create a wedge of appropriate size.

The cartilage block removed from the window was used as a template, with 2 to 3 mm of Silastic allowed to protrude beyond it on all four sides. It was also used to position and measure a "key" or lateral extension of Silastic on the lateral surface of the carved wedge to fix the block in the pocket (see Figure, D). A posterior corner was cut away from the Silastic wedge to allow for the entry of the nerve-muscle pedicle. The wedge was then compressed and inserted into the pocket through the window and positioned so that the lateral "key" was locked into the window (see Figure, E).

The resulting voice and airway were then assessed. On the two occasions that the airway seemed to be compromised by the implant, the Silastic was removed, trimmed, and reinserted. On one occasion it was clear that voice improvement was inadequate. The block was removed and a new, slightly larger one was carved and inserted. The wound was closed over a small Penrose or rubber band drain. Broad spectrum antibiotics were given for 48 to 72 hours. Patients who underwent any type of laryngeal framework operation[7,8] were initially kept in the hospital overnight, but after the first 50 consecutive patients (not all included in this study) suffered no complications in the first 24 hours they were thereafter permitted to go home on the night of the operation. Postoperative voice assessment was carried out 2 weeks, 3 months, and 6 months after the operation.

RESULTS

All patients developed marked improvement in vocal strength and ability to sustain speech, varying from immediately on the operating table to 3 weeks postoperatively. Not infrequently, what was an initially excellent voice result at operation would deteriorate for various periods of time before gradually restabilizing at improved levels. All of these patients have sustained the improvement to the present. All of the 29 patients had successful medialization of the vocal fold with significant improvement in the voice, and 19 of the 29 (66%) had further improvements in quality and pitch control 2 to 6 months later.

There were no immediate complications. Airway obstruction occurred in one patient 72 hours after the operation (48 hours after discharge). A tracheotomy tube was inserted, and it was successfully removed without further incident 1 week later. The patient's voice result was excellent. There was extrusion of one of the Silastic implants 9 months after the operation. The patient coughed up the implant, but her voice improvement has been sustained despite loss of the Silastic.

All of the patients have been followed up for at least 6 months, beyond which time no patient in our previous experience has shown onset of motor activity after attempted reinnervation.[5] Nineteen of the 29 patients are judged to show evidence of successful reinnervation (66%), as evidenced by visible tensing, increased muscle volume, and improved turgor of the vocal fold. There has been subjective and objective improvement in voice over that which was achieved by mechanical medialization alone in all of these cases, but not in the patients who showed no evidence of successful reinnervation. Onset of perceived secondary improvement in voice varied from 2 months to 5 months after the operation. Detailed phonatory analysis of this group of patients will be the subject of a subsequent communication.

DISCUSSION

Vocal fold medialization by Silastic or other implantation has long been known to afford good possibilities for voice improvement. Recent improvements in diagnosis, materials, technique, and documentation have permitted its employment in patients who are not likely to achieve reliably satisfactory results with Teflon injection. Since it is now clear that it can be done under local anesthesia and as an outpatient procedure, it may begin to replace Teflon injection for many patients, especially because it can be easily removed, whereas Teflon cannot.

Nerve-muscle pedicle reinnervation has been shown to succeed in restoring not only adduction of the vocal fold, but also the ability to tense the muscles and thus to control pitch.[5,6] Theoretically, at least, it should permit the closest possible return to "normal" function that can be achieved with present technology. It has suffered from the built-in delay of 2 to 6 months after the operation before any improvement may be noted. If it can be combined with Silastic implant medialization, the patient can have immediate voice improvement while awaiting the onset of further improvement in quality and pitch control. Although definitive voice analysis is not yet complete, it is clear that many of these patients have experienced further improvement in voice commencing some weeks or months after the initial postoperative results. Since no individual experienced any complication from the reinnervation process itself, it seems reasonable to continue to combine these two procedures for properly selected patients.

CONCLUSIONS

Implantation of Silastic under local anesthesia for medialization of a unilateral immobile vocal fold is a relatively safe and effective way to restore vocal loudness and sustainability. It can be combined with nerve-muscle pedicle reinnervation as a single procedure under local anesthesia that can provide improved pitch control and voice quality in selected patients without increased cost or risk.

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26TH POSTGRADUATE COURSE IN EAR SURGERY

The 26th Postgraduate Course in Ear Surgery will be held from April 7-12, 1991, in Nijmegen, the Netherlands. For further information and registration form, please write to: Prof Dr P. van den Broek, University Hospital Nijmegen, Department of Otorhinolaryngology, PO Box 9101, 6500 HB Nijmegen, the Netherlands; Telefax 80-540251.

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CARE OF THE PROFESSIONAL VOICE

The Voice Foundation's 20th Annual Anniversary Symposium on Care of the Professional Voice will be held July 14-19, 1991, at the Warwick Hotel in Philadelphia, Pennsylvania. For further information, contact The Voice Foundation, 1721 Pine Street, Philadelphia, PA 19103; (215) 735-7999.

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OBJECTIVE VOICE MEASUREMENTS & STANDARDS

A course entitled Objective Voice Measurements & Standards will be held July 22-23, 1991, at the Warwick Hotel in Philadelphia, Pennsylvania. For further information, contact The Voice Foundation, 1721 Pine Street, Philadelphia, PA 19103; (215) 735-7999.

Ann Otol Rhinol Laryngol 99:1990

IMMUNOHISTOCHEMICAL INTERPRETATION OF EARLY EPITHELIAL DISORDERS OF PYRIFORM SINUS

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Expression of cytokeratins (CKs) was investigated immunohistochemically by use of monospecific monoclonal anti-CK antibodies in normal epithelia of pyriform sinus and epithelial lesions such as simple hyperplasia, different degrees of dysplasia, in situ carcinoma, and invasive carcinoma. In normal epithelium, strong expression of CK-19 was consistently observed only in the basal layer as basic CK, while expression of CK-13 showed a completely reverse pattern, being expressed only in suprabasal layers as stratification-related CK. Characteristic changes in expression pattern of these two CKs were observed in accordance with the degree of epithelial disorders and differentiation of carcinoma. Cytokeratin 1, as keratinization-associated CK, was observed only in keratinized cells of hyperplastic epithelia and well-differentiated carcinomas. These findings may be useful in evaluating epithelial disorders and classifying carcinomas more objectively, and may assist earlier detection of carcinoma when used with standard histologic techniques.

KEY WORDS — cytokeratin, epithelium, immunohistochemistry, monoclonal antibody, pyriform sinus carcinoma.

INTRODUCTION

Despite advances in a combination of surgery, chemotherapy, and radiotherapy, the 5-year survival rate for pyriform sinus carcinoma (PSC) continues to be less than 30% in most institutions over the world. Since there are no early warning symptoms or signs, most cases are detected and treated when more advanced than stage III. However, by the use of an improved fiberscope that attaches a disposable hood to prevent undesirable contact of the tip with the mucosa, epithelial abnormalities suggestive of biopsy can be screened under topical anesthesia for the early detection of PSC.

On the other hand, histologic evaluation of the biopsied specimen stained with hematoxylin and eosin is not always an easy task even for trained pathologists, and more objective methods to enable a clear diagnosis have been explored. Investigation of biochemical changes that may accompany morphologic abnormalities should be considered.

Cytokeratin (CK) is one of the intermediate filaments composing the cytoskeleton of epithelial cells. It has been noted that the human CKs have a family of 19 subclasses that polymerize to form cytoplasmic filaments in epithelial cells and epithelial-derived carcinomas, and that only a few subclasses are usually expressed by an individual epithelial cell. It is also known that the variability in expression of different subclasses is related to organs, cell types, and cellular differentiation, and that the expression pattern produced by normal epithelial cells changes upon malignant transformation.[1-7]

From these standpoints, the CKs were used to investigate the possible biochemical changes in the pyriform sinus epithelia that may originate during transformations between normal epithelium, simple hyperplasia, dysplasia, in situ carcinoma, and invasive carcinoma.

MATERIALS AND METHODS

Tissues. During the past 2 years, 23 biopsy specimens were obtained with a rigid scope under general anesthesia from the pyriform sinuses of patients who showed mild abnormalities of the epithelium such as irregular or erosive lesions with a flat surface, warty white lesions, or slight stiffness to touch with the scope at fiberscopic screening. Seven other samples from patients with PSC were harvested at the definitive operation directly from the massive tumor and also from macroscopically normal epithelium adjacent to the tumor. A total of 30 pathologic samples, then, were investigated in this series.

Eighteen samples were obtained as a control from the patients with normal pyriform sinuses at their autopsies or during operations such as total laryngectomy, lateral pharyngotomy, or pharyngeal flap operation. Two of them were excluded because the patients had a history of previous radiotherapy for neck lesions.

These samples were fixed in 85% ethanol for 48 hours, embedded in paraffin, and then sliced into 15 consecutive sections 4 μm thick.

Histologic Staining and Classification. One of these sections from each sample was stained with hematoxylin and eosin, evaluated histologically, and classified into one of five groups according to established histologic criteria[8-10]: normal epithelium, simple hyperplasia, dysplasia of different

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Presented at the meeting of the American Laryngological Association, Palm Beach, Florida, April 28-29, 1990.

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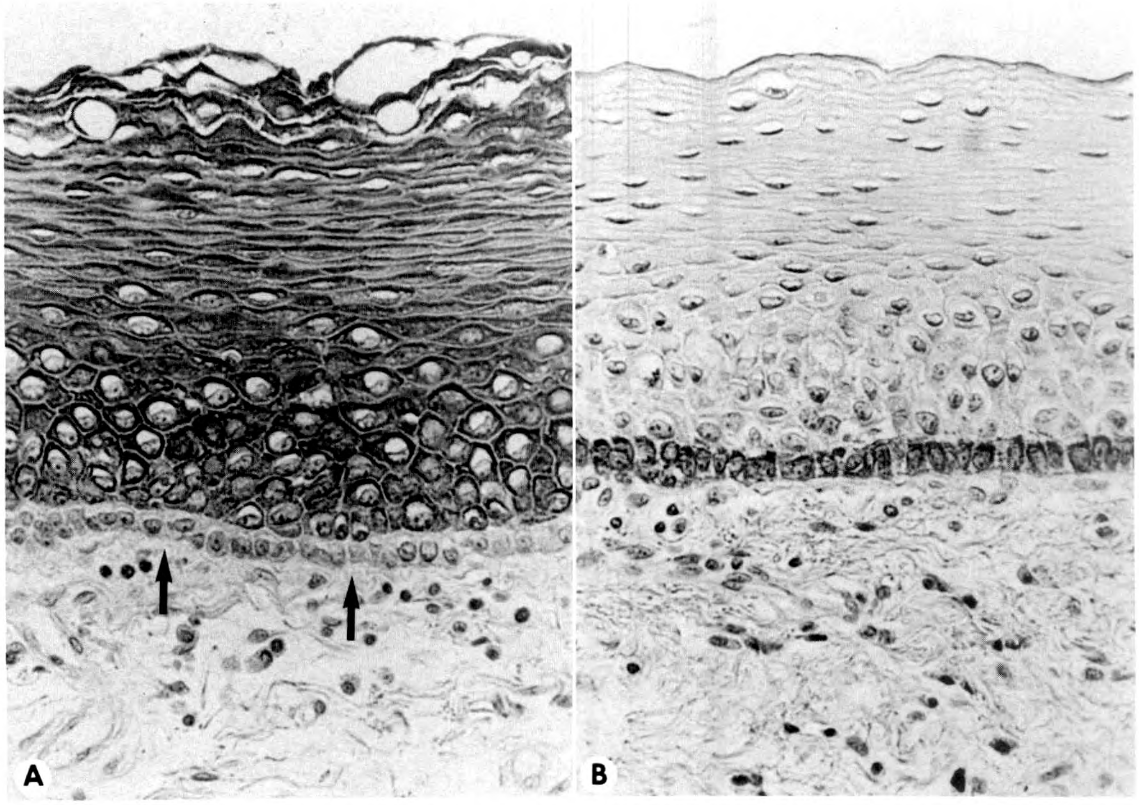

Fig 1. Normal epithelium. A) CK-13 is expressed strongly in whole layers except for basal layer (arrows). B) Expression of CK-19. Strong expression is observed only in basal layer. It is reduced in suprabasal layers and completely disappears in outer layers.

grades, in situ carcinoma, and invasive carcinoma.

Immunohistochemical Staining. The other sections were examined immunohistochemically by means of the avidin-biotin-peroxidase complex (ABC) technique[11] using monospecific monoclonal anti-CK antibodies. The Elite ABC Kit (Vector, United States) was used for the ABC technique. Before staining, sections were incubated in hydrogen peroxide to block endogenous peroxidase and treated with trypsin for better reaction to antibodies. Diaminobenzidine tetrahydrochloride (DAB, Zymed, United States) was used as the chromogen, and hematoxylin was used to counterstain nuclei. Results were investigated microscopically and compared with those of hematoxylin and eosin staining. Positive immunostaining was defined as a clear brown staining of the cytoplasm, and the intensity of expression was estimated on the basis of its density.

Antibodies. Ten kinds of monoclonal anti-CK antibodies were used that are now commercially available in Japan. They are monospecific for each subclass of CKs with a different molecular weight: CK-1, -3, -7, -8, -10, -11, -13, -14, -18, and -19.

They are MA-904 (Enzo, United States, diluted 1:2,000) for CK-1 with the highest molecular weight of 68 kD, AE-5 (Progen, Federal Republic of Germany, diluted 1:100) for CK-3 of 63 kD, RPN-1162 (Amersham, England, diluted 1:100) for CK-7 of 54 kD, MA-902 (Enzo, diluted 1:2,000) for CK-8 of 52.5 kD, RKSE-60 (Sanbio, the Netherlands, diluted 1:10) for CK-10 of 56.5 kD, CK-8.60 (BioMakor, Israel, diluted 1:200) for CK-11 of 56 kD, Ks-13.1 (Progen, diluted 1:200) for CK-13 of 54 kD, CKB-1 (BioMakor, diluted 1:500) for CK-14 of 50 kD, Ks-18.18 (Progen, diluted 1:200) for CK-18 of 45 kD, and Ks-19.1 (Progen, diluted 1:200) for CK-19, with the lowest molecular weight of 40 kD. We also used anti-CK-6 antibody supplied by Professor Elaine V. Fuchs, Howard Hughes Medical Institute Research Laboratories, Chicago, Ill.

RESULTS

Histologic Classification. Forty-six samples were evaluated on the basis of morphology by hematoxylin and eosin staining and classified into five groups: 22, normal epithelia; 3, simple hyperplasia; 9, dysplasia of different grades; 5, in situ carcinoma; and 7, invasive carcinoma.

According to the degree of cellular atypia and loss of polarity, nine with dysplasia were subdivided into four mild, two moderate, and three severe lesions. All five in situ carcinomas were evaluated as nonkeratinized disorders with bizarre morphologic characteristics. Two of them were found in macroscopically normal epithelia harvested from the patients with PSC. Seven invasive squamous cell carcinomas were graded as three well, three moderately,

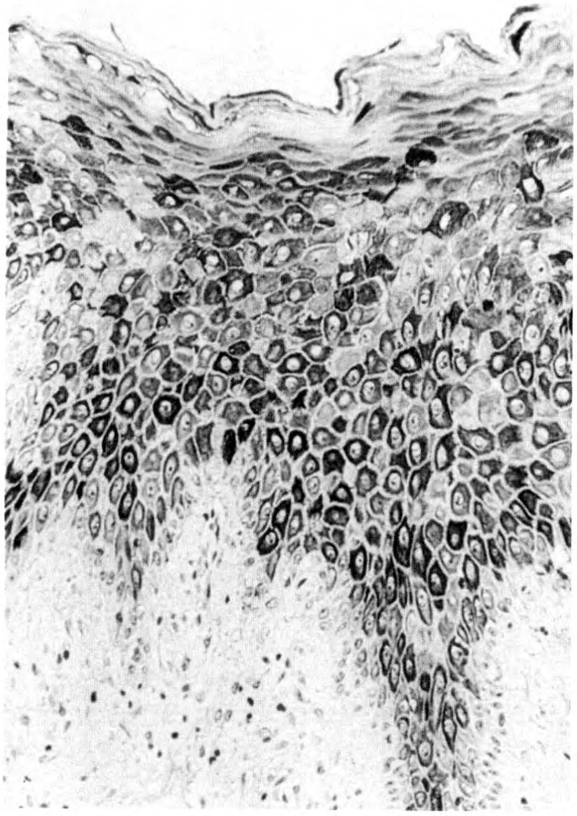

Fig 2. Reaction with CK-1 is observed in well-keratinized hyperplastic epithelium.

and one poorly differentiated.

Normal Epithelium. In the normal epithelium, only two subclasses of CK were immunohistochemically observed. They were CK-13 and -19, and were expressed consistently in all 22 samples. Expressions of any other subclasses, including CK-1, -3, -7, -8, -10, -11, -14, and -18, were never observed in these samples.

It is noteworthy that these two subclasses have apparently reverse patterns of expression. Cytokeratin 13 was expressed within the whole thickness of the epithelium except for the basal layer, and the intensity increased in the superficial layers (Fig 1A). On the contrary, strong expression of CK-19 was observed only in the basal layer, was apparently reduced in the suprabasal layers, and completely disappeared in the superficial layers (Fig 1B).

Simple Hyperplasia. In all three specimens with simple hyperplasia, the same subclasses were expressed as those in the normal epithelium. Reaction with CK-13 was observed throughout the layers except for the basal layer, just as in the normal epithelium. But the expression pattern of CK-19 was somewhat different from that in the normal epithelium. Reaction with CK-19 was uniformly observed in whole layers, although it was not remarkable in the suprabasal layers, and a positive reaction with CK-1 was observed in a specimen with well-kerati-

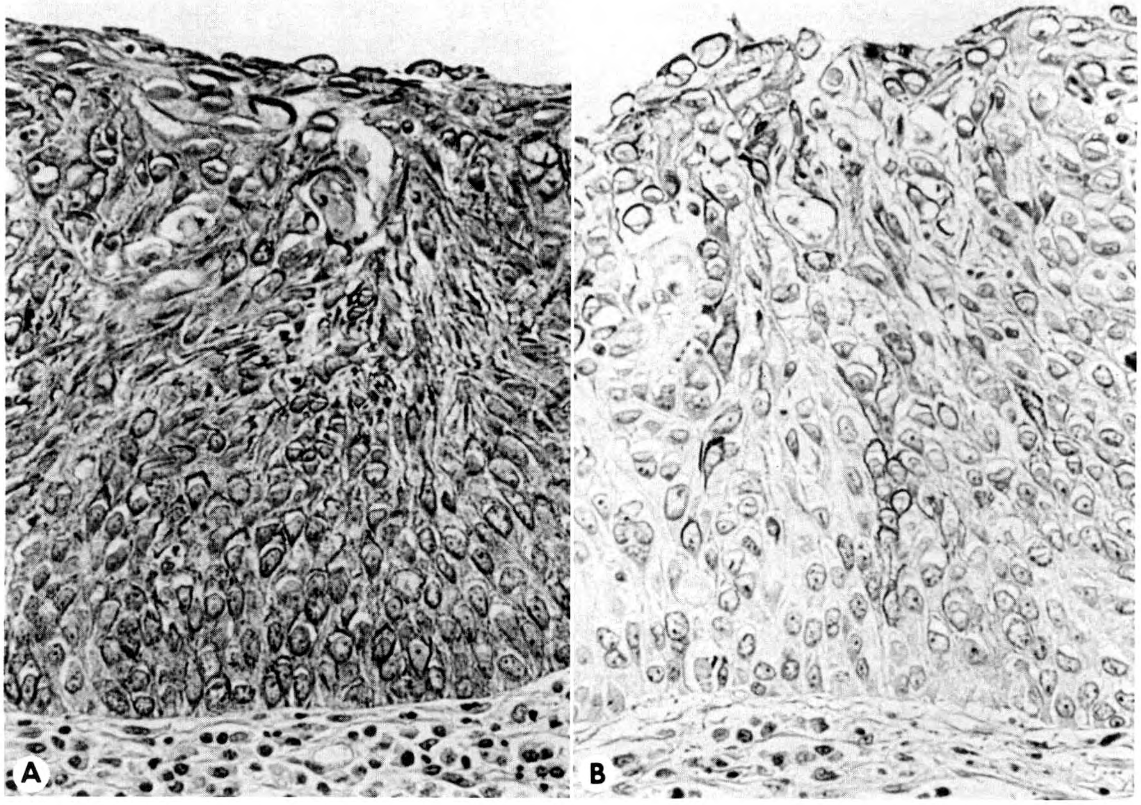

Fig 3. Severe dysplasia. A) With marked disturbance of polarity. Expression of CK-19 is observed in almost all layers. B) Very weak, scattered reaction with CK-13.

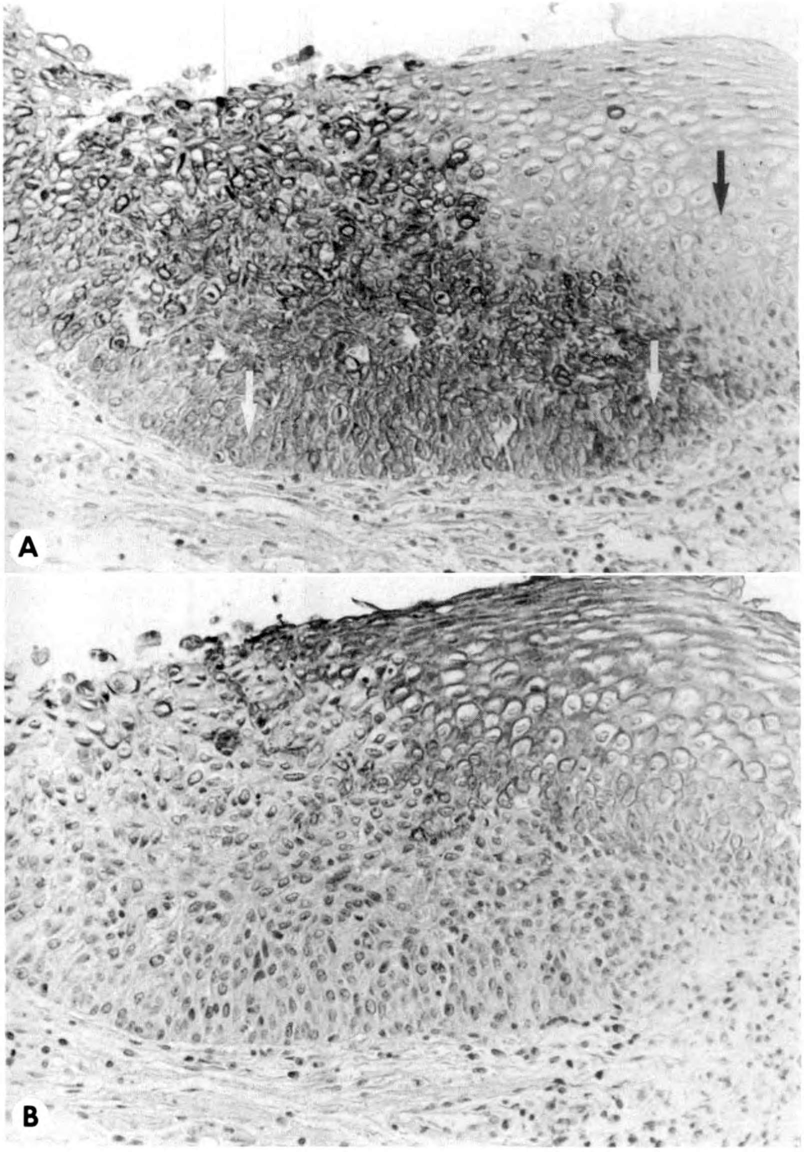

Fig 4. In situ carcinoma. A) CK-19 is strongly expressed in portion of in situ carcinoma (white arrows), but not in hyperplasia except for basal layer (black arrow). B) Same lesion, showing expression pattern of CK-13 that is in striking contrast to that of CK-19 in A.

nized hyperplastic epithelium (Fig 2). No other subclasses were expressed.

Dysplasia. Reactions with CK-13 and -19 were also demonstrated in all nine dysplastic epithelia, and their expression patterns were distinctively different from each other depending upon the grades of dysplasia. Cytokeratin 19 was consistently positive in whole layers, and its intensity was stronger with increasing grades of dysplasia. It was strongly expressed in the basal and parabasal layers and a few inner layers and weakly expressed in the outer layers in all four specimens with mild dysplasia. In moderate dysplasia, it was expressed strongly in almost the entire inner half of the epithelium. In severe dysplasia, a stronger expression of CK-19 was distinctly observed in more layers of the epithelium, and strongly positive cells were found scattered even in the outer layers (Fig 3A).

On the contrary, the expression of CK-13 decreased in proportion to the grade of dysplasia. In mild dysplasia, positive cells were observed with the same expression pattern as the normal epithelium and specimens with simple hyperplasia. In moderate dysplasia, a reaction was found in the outer half to one third of the layers, while a very weak reaction was found scattered irregularly through the layers in severe dysplasia (Fig 3B). Expression of any other subclasses was not observed.

In Situ Carcinoma. In all five in situ carcinomas, a strong reaction with CK-19 was observed in the full thickness of the involved epithelium. Reaction with CK-13, on the contrary, was completely negative in three samples, and only a few positive reactions were found, irregularly scattered, in the other two samples. The intensity was much weaker than in those with dysplasia. In a section showing in situ carcinoma in continuity with hyperplasia, these findings were graphically demonstrated (Fig 4). No other subclasses were expressed at all.

Invasive Carcinoma. Whereas CK-19 was strong-

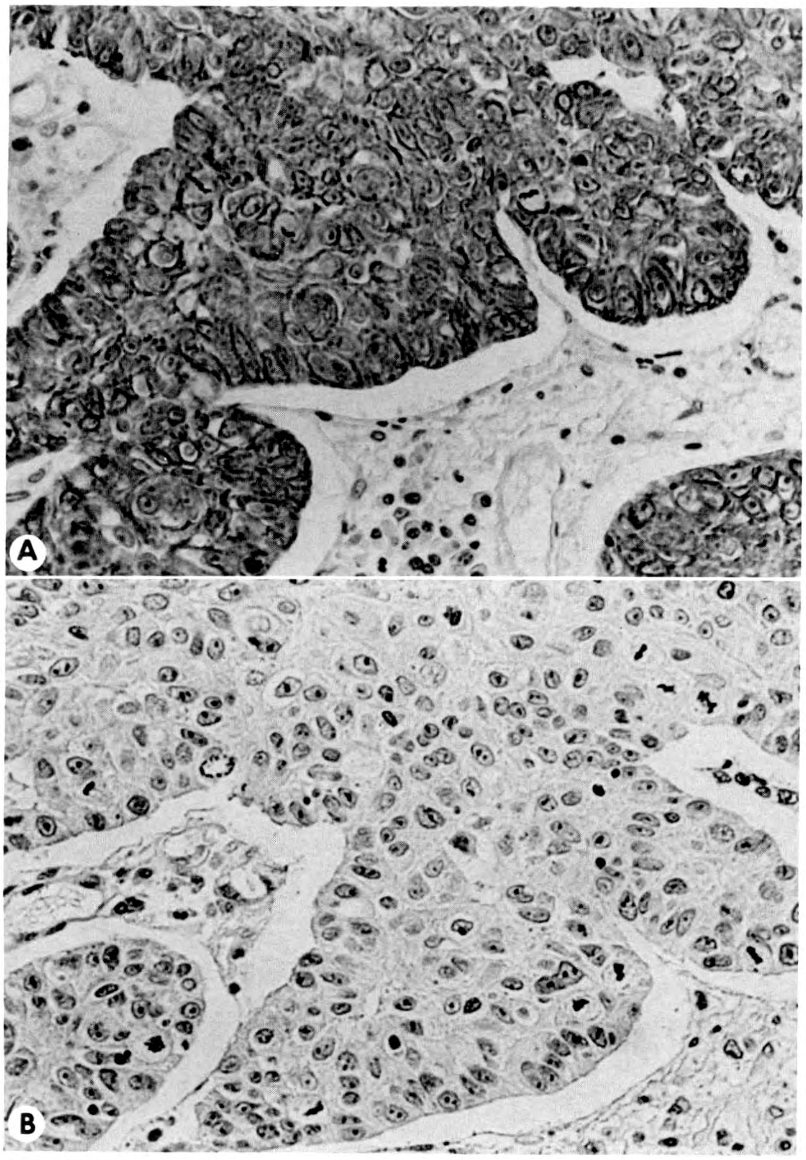

Fig 5. Poorly differentiated carcinoma. A) CK-19 is strongly positive in all cells. B) Same lesion, with CK-13 completely negative.

ly positive in all cells in a sample of poorly differentiated carcinoma, CK-13 was completely negative throughout the lesion (Fig 5).

In all three moderately differentiated carcinomas, CK-19 was also strongly positive, even in well-keratinized cells scattered mostly in the center portion of the nests. A positive reaction with CK-13 was also observed, but it was found only in well-keratinized cells (Fig 6).

Three well-differentiated carcinomas, on the other hand, showed a striking contrast to these findings. Reaction with CK-19 was not observed at all, but positive cells with CK-13 were found scattered, showing a heterogeneous staining pattern. A strong reaction with CK-1 was observed consistently in all three samples (Fig 7). It was expressed in well-keratinized cells showing distinctive intercellular bridges. It is noteworthy that CK-1 was never expressed in the normal epithelium or in any other lesions except for keratinized hyperplastic epithelium. No other subclasses were expressed.

DISCUSSION

It has been reported that CK-13, together with CK-4 as a keratin pair, is one of the major components of normal human esophageal epithelium[1,2,7,12-14] and is expressed in the suprabasal layers as the stratification-related CKs.[5,15] There is no report on the expression pattern of CKs in normal hypopharyngeal epithelia, but our results are in good agreement with the reports on the esophagus. Grace et al[13] studied the expression pattern of CKs in esophageal carcinomas chemically by immunoblot analysis of electrophoretically separated protein extracts and reported that CK-13 is frequently present in reduced, if detectable, levels, and that CK-14, -15, and -17 substantially increase; they concluded that these changes in CK synthesis seem to have a diagnostic value, since the latter three CKs are seldom observed in normal epithelia. Although we could not attest to the expression of these three sub-

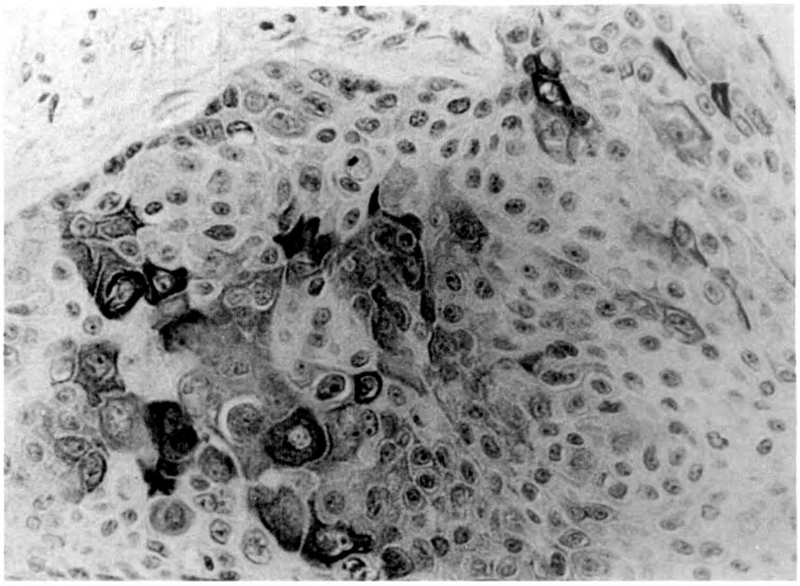

Fig 6. In moderately differentiated carcinoma composed of keratinized cells without pearl formation, reaction with CK-13 is found scattered only in well-keratinized cells.

classes because of difficulty in obtaining qualified antibodies, the immunohistochemical technique we used with paraffin-embedded materials has the advantage in demonstrating the localization and intensity of positive reactions and in comparing the results with those of hematoxylin and eosin stainings. Our results showed that the expression pattern of CK-13 changes definitely in each morphologic stage and in each degree of differentiation of carcinomas, so it may be useful as an improved technique for differential diagnosis.

Also by chemical analysis using gel electrophoresis, Leube et al,[5] Banks-Schlegel and Harris,[12] and Grace et al[13] failed to identify CK-19 in normal esophageal epithelia, and Grace et al[13] and Wu et al[16] reported that CK-19 appears only in cultured esophageal cells and increases steadily through several rounds of culturing. Quinlan et al[17] and Nagle et al,[14] on the other hand, identified minor amounts of CK-19 using the same technique. Bartek et al[3] investigated the expression pattern of CK-19 immunohistochemically in each part of human epithelia and reported that it is expressed mainly in the basal cell in nonkeratinizing squamous epithelia, forming a keratin pair with CK-5. Our results also showed that CK-19 is one of the most fundamental CKs of the pyriform sinus epithelia and is routinely expressed in the basal cell.

In the normal epithelium, reaction with CK-13 was not observed in the basal layer, but in all suprabasal layers, and the expression of CK-19 showed a completely reverse pattern. These results indicate that distinctive changes in protein synthesis may originate in association with proliferation of basal cells into parabasal cells as a process of terminal differentiation controlled by an unknown mechanism.

Considerable changes in the expression pattern of

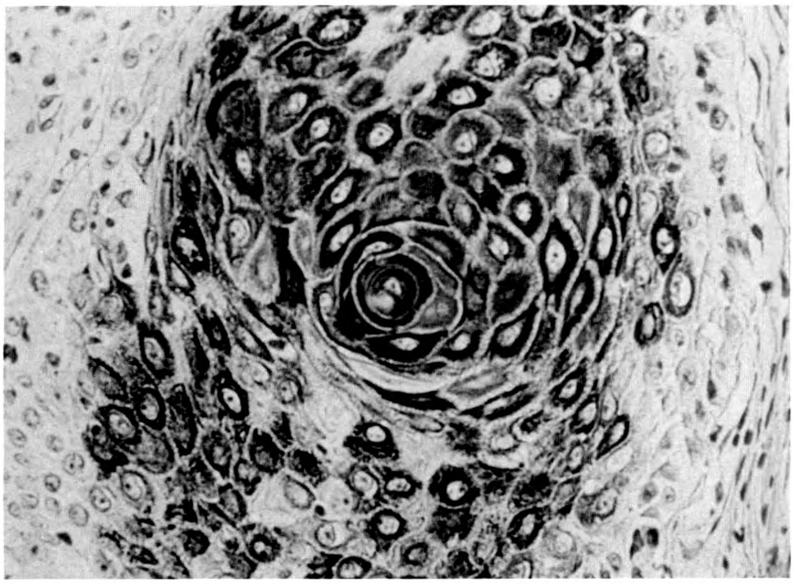

Fig 7. In well-differentiated carcinoma, strong reaction with CK-1 is observed in well-keratinized cells with marked intercellular bridges.

CK-13 and -19 were observed in abnormal epithelia and carcinomas. A dramatic reduction or complete loss of CK-13 was demonstrated in dysplastic epithelia, in situ carcinomas, and poorly differentiated carcinomas or nonkeratinized carcinoma cells. These results indicate that negative cells may have failed to activate the antigenic determinant for CK-13 during proliferation from the basal cell and maintain the immunochemical characteristics of the basal cell probably by a defect in the pathway of the terminal differentiation. The variability of the expression pattern, closely related to the degree of abnormalities, may be relevant to the degree of delayed differentiation from the basal cell. Probably by the same mechanism, the antigenic determinant for CK-19 in the basal cell may be reduced in the suprabasal layers in the normal epithelium, but may be retained in abnormal epithelia in relation to the degree of abnormalities.

In in situ carcinomas, strong expression of CK-19 and an almost complete loss of CK-13 were consistently observed. These findings suggest that most primary PSCs display a defect in the program of terminal differentiation and then maintain the same immunochemical characteristics as the basal cell. Poorly differentiated carcinomas showed the same expression pattern as in situ carcinomas. The results may also suggest that immunochemically immature carcinoma cells continue to proliferate without a program of differentiation. Keratinized cells of moderately differentiated carcinomas, on the other hand, expressed CK-13; this finding may indicate that a process of differentiation has originated. Whereas reactions with CK-13 were observed, a complete lack of CK-19 was a consistent finding in well-differentiated carcinomas. Furthermore, CK-1, which has been reported[2] as one of the keratinization-associated CKs of the skin, was demonstrated in well-keratinized carcinoma cells. Since we could never observe CK-1 in normal epithelia, these results may indicate that the differentiation program is substantially progressing together with an abnormal process of keratinization.

These characteristic changes were consistently demonstrated by the immunohistochemical technique using paraffin sections of biopsied material. This technique may be useful in evaluating epithelial disorders in the pyriform sinus and may result in earlier detection and objective classification of PSC when used in conjunction with standard pathologic techniques.

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Ann Otol Rhinol Laryngol 99:1990

AUDITORY BRAIN STEM IMPLANT: EFFECT OF TUMOR SIZE AND PREOPERATIVE HEARING LEVEL ON FUNCTION

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The auditory brain stem implant is an investigational device designed to provide hearing sensations to patients without functioning auditory nerves. We analyzed results from 17 implants in 15 patients to determine if tumor size or preoperative hearing level might be related to proper device function. We found no significant correlation between preoperative hearing level or tumor size and device function. We also found no significant correlation between preoperative hearing level and tumor size in these 15 patients.

KEY WORDS — acoustic tumor, auditory threshold, brain stem, implant.

INTRODUCTION

The auditory brain stem implant (ABI) is designed to provide auditory sensations by electrically stimulating the cochlear nucleus complex.[1,2] The device is under investigation for use in bilateral acoustic tumor patients who become deaf from sectioning of the eighth nerve during tumor removal. Deafness in such patients is often unavoidable because of the invasive nature of bilateral tumors[3] and involvement of the cochlear blood supply.[4,5] The tumors may become quite large (5 cm or more), because removal often is postponed to prolong use of remaining hearing. During excision of large tumors, surgeons have observed distortion and possible damage to anatomic landmarks critical to the proper placement of the ABI. A preliminary review of implant results in 10 patients suggested the hypothesis that tumor size and preoperative hearing level are related to presence of auditory sensations from the device. Tumor size might affect device function because large tumors are seen on radiographs to compress and displace the brain stem by as much as 2.5 cm, resulting in anatomic distortions and possible damage.[6] Preoperative hearing level might be a possible indicator of neural damage. We analyzed results of 17 implants in 15 patients to determine if tumor size or preoperative hearing level might be related to proper device function, and thus if patients with smaller tumors or better preoperative hearing may be better candidates for implantation.

SUBJECTS AND METHODS

We reviewed the charts of 15 patients with bilateral acoustic tumors who received an ABI during tumor excision from 1979 to 1989. There were nine men and six women ranging in age from 18 to 62 years. Four received the device when their first tumor was removed. Two patients also received a second implant on the contralateral side after percutaneous plug infections led to termination of use of the first device. Therefore, we reviewed data on a total of 17 implanted devices.

Twelve of 17 implants resulted in auditory sensations and discrimination of speech and environmental sounds at levels similar to those of adult 3M/House cochlear implant users.[2] Of these 12, 4 worked initially but later failed after breaks in electrode wires (two patients) or percutaneous plug infections (two patients). Five other implants produced either no hearing sensation at all, or facial or throat sensations. We classified implants into two groups: functional, defined as providing only auditory sensations for any length of time; and nonfunctional, defined as providing no auditory sensations or as evoking facial or throat sensations.

From the patient charts, we obtained the preoperative pure tone average auditory threshold in decibels hearing level (HL)[7] at 500, 1,000, and 2,000 Hz measured by standard audiometric techniques. Tumor size was determined by measurement of the largest intracranial extension on radiographic images.

RESULTS

The overall mean preoperative pure tone average was 71 dB HL (SD = 24.8 dB), and overall mean acoustic tumor size was 3.9 cm (SD = 1.2 cm). Twelve implants were classified as functional and five as nonfunctional. Mean preoperative hearing level was 70 dB HL for the functional group (SD = 26.9 dB) and 75 dB HL for the nonfunctional group (SD = 21.3 dB). Hearing levels varied widely within each group. Mean tumor size was 3.7 cm for the functional group (SD = 0.81 cm) and 4.6 cm for the nonfunctional group (SD = 1.7 cm).

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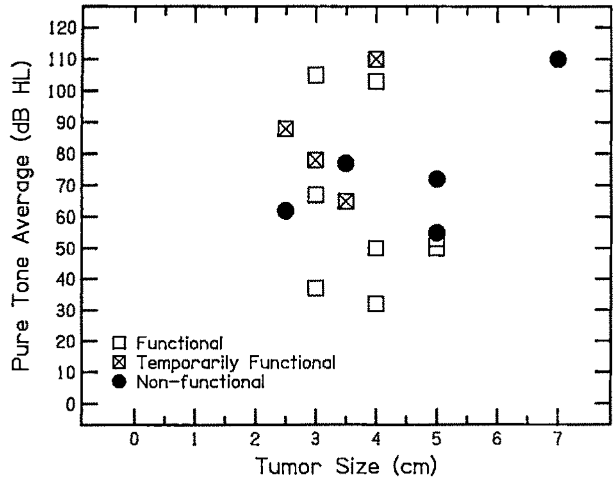

Preoperative auditory thresholds in decibels hearing level (mean of 500, 1,000, and 2,000 Hz) according to acoustic tumor size. Implants are identified as functional; temporarily functional, ie, devices that worked initially but later ceased to function; or nonfunctional.

The Figure plots preoperative pure tone average by tumor size with implant function as a parameter. The four devices that eventually ceased to function are identified separately.

To determine possible predictive value of the preoperative factors, we analyzed the correlations (point biserial) between preoperative hearing level, acoustic tumor size, and implant function. We also analyzed the correlation between preoperative hearing level and tumor size. For descriptive purposes, we included implant results from both sides of patients with bilateral implants in the calculation of correlation coefficients. The correlation between preoperative hearing level and ABI function was +.10; between tumor size and function, +.37; and between preoperative hearing level and tumor size, +.10. For inferential purposes, we also calculated correlation coefficients excluding one ear at random from each bilateral implant case because independence of each side could not be assured. The correlation between preoperative hearing level and function was +.11 ($p = .35$); between tumor size and ABI function, +.34 ($p = .11$), and between preoperative hearing level and tumor size, +.12 ($p = .34$).

DISCUSSION

Many of these bilateral tumor patients had poorer preoperative hearing at the time of tumor removal than unilateral tumor patients.[5,8] Bilateral tumors also were larger than unilateral tumors,[5,8,9] but similar in size to those in another report of bilateral tumor size.[4] The size difference may be attributed to a tendency for bilateral patients to present when tumors are relatively large[5,10] and to postponement of tumor excision to delay onset of deafness. Although preoperative hearing levels were poorer and tumor sizes larger in the studied patients, the correlation between tumor size and hearing loss was low. This finding also has been reported in patients with unilateral tumors[8] and may reflect variations in tumor origin (intracanalicular or extracanalicular) or variations in brain stem anatomy.[9]

Our findings do not support our initial hypothesis that preoperative hearing level or tumor size is related to the presence of auditory sensations from the ABI. Rather, our results show no significant relationship between these factors and imply that patients with large tumors or very poor preoperative hearing should still be considered as possible candidates for the ABI.

ACKNOWLEDGMENTS — The authors thank Pamela Carter, RN, for assistance in data collection; Donald W. Nielsen, PhD, and Robert V. Shannon, PhD, for comments on the manuscript; and House Ear Clinic for audiologic services.

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Ann Otol Rhinol Laryngol 99:1990

COCHLEAR IMPLANT FLAP COMPLICATIONS

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In a series of 52 patients who received cochlear implants, 4 patients suffered flap complications (7.7%). The problems encountered involved the postauricular flap and were usually minor in nature. None required explantation as a direct result of these complications. Flap ischemia in a patient with Cogan's syndrome and vasculitis, two cases of suture extrusion with one having exposure of the implant, and a case of receiver unit magnet extrusion repaired with a vascularized pericranial flap based upon temporalis muscle are presented. Flap design in patients who have had postauricular incisions demands special consideration. Principles useful for avoiding complications as well as their management are discussed.

KEY WORDS — cochlear implant, postoperative complications, surgical flaps.

INTRODUCTION

Although the postauricular and parietal-occipital scalp skin areas are well vascularized, the conflicting demands of flap viability and optimal coil transmission through thinned skin compressed by magnetic forces in cochlear implant recipients can cause flap complications. This is especially true in instances of already compromised circulation, such as from prior operation in the same region.[1] In a comprehensive survey of complications associated with the use of the Nucleus multichannel cochlear implant, Cohen et al[2] found 22 cases of flap breakdown or infection in a total of 459 operations. Nine of these required explantation. Eighty percent of flap complications transpired within the first three operations performed by individual surgeons. Nevertheless, even experienced operators must take care in designing and preparing skin flaps for cochlear implants, particularly in those patients with prior ear operations or cochlear implantation. A recent survey by Parisier et al (unpublished data, 1989) reveals 130 of 1,175 patients (11%) had failed implants — including 19% of 569 3M/House devices and 3.5% of 606 Nucleus implants — the majority of whom were candidates for reimplantation. This paper presents four skin flap complications encountered by the senior author (S.C.P.) in a series of 52 cochlear implants (7.7%).

CASE REPORTS

Case 1. A 50-year-old woman presented with a history of binaural sensorineural hearing loss that had progressed for 5 years, until 8 months prior, when sudden worsening occurred and hearing aids were no longer helpful. An audiogram confirmed binaural deafness, with magnetic resonance imaging and computed tomography (CT) results being normal, without cochlear dysplasia or ossification. Cochlear implantation with a Nucleus 22 multichannel device was performed in June 1988 by use of a standard anteriorly based flap. The immediate postoperative course was uneventful, and the external coil was applied 2 months later.

In December 1988, extrusion of the internal magnet through the center of the otherwise intact skin flap was noted (Fig 1A). Revision was accomplished by extending the anterior limb of the original incision to allow elevation of a large pericranial flap based upon the posterior half of the temporalis muscle (Fig 1B). The internal coil and magnet were rotated anteriorly and secured away from the skin perforation, which was oversewn. Complete coverage of the receiver unit with the thin pericranial flap rotated posteroinferiorly was performed to prevent reextrusion (Fig 1C). After an episode of skin erythema overlying the internal magnet 3 months after revision, treated by reducing magnet strength and wearing time, the patient was doing well 14 months following pericranial flap repair.

Case 2. A 29-year-old man in 1971 developed fluctuating bilateral sensorineural hearing loss, vertigo, and tinnitus. Cogan's syndrome was diagnosed in 1974 with the discovery of interstitial keratitis. After progression to binaural deafness, left cochlear implantation with an original House Sigma single-channel device was performed in 1978. Despite steroid treatment, in 1980 his vasculitis worsened, with Raynaud's disease, congestive heart failure caused by an isolated left main coronary artery stenosis requiring a coronary bypass operation, and a transient ischemic attack with central aphasia and pulse deficits of the left upper extremity. He continues to this day to receive steroid therapy.

In 1983, the patient underwent right cochlear implantation with a House/3M single-channel Alpha magnetized device by the senior author (S.C.P.) after preoperative assessment with an audiogram,

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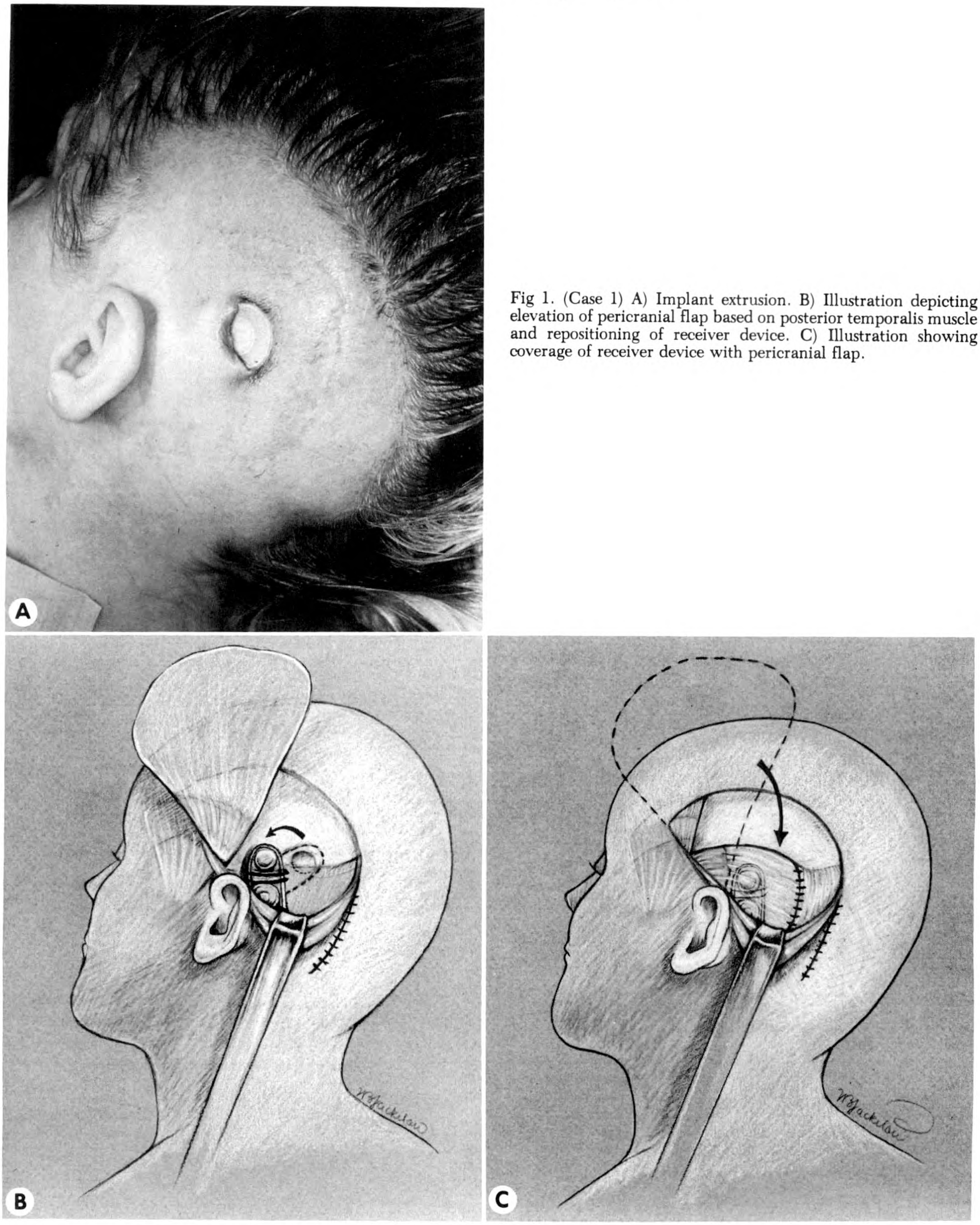

Fig 1. (Case 1) A) Implant extrusion. B) Illustration depicting elevation of pericranial flap based on posterior temporalis muscle and repositioning of receiver device. C) Illustration showing coverage of receiver device with pericranial flap.

electronystagmography, and a CT scan. Although his communication skills were improved, the patient was unable to use a telephone, since he lacked any open-set discrimination. After extensive discussion and left promontory stimulation showing good responses, the patient elected to upgrade the left ear device with a Nucleus 22 multichannel implant in May 1987. In order to accommodate the larger Nucleus device, a separate, posterosuperiorly staggered incision was used to create an anteriorly based skin flap (Fig 2A). The area between the old and new incisions became increasingly cyanotic during the next 2 weeks (Fig 2B). After superficial sloughing, this area healed well by secondary inten-

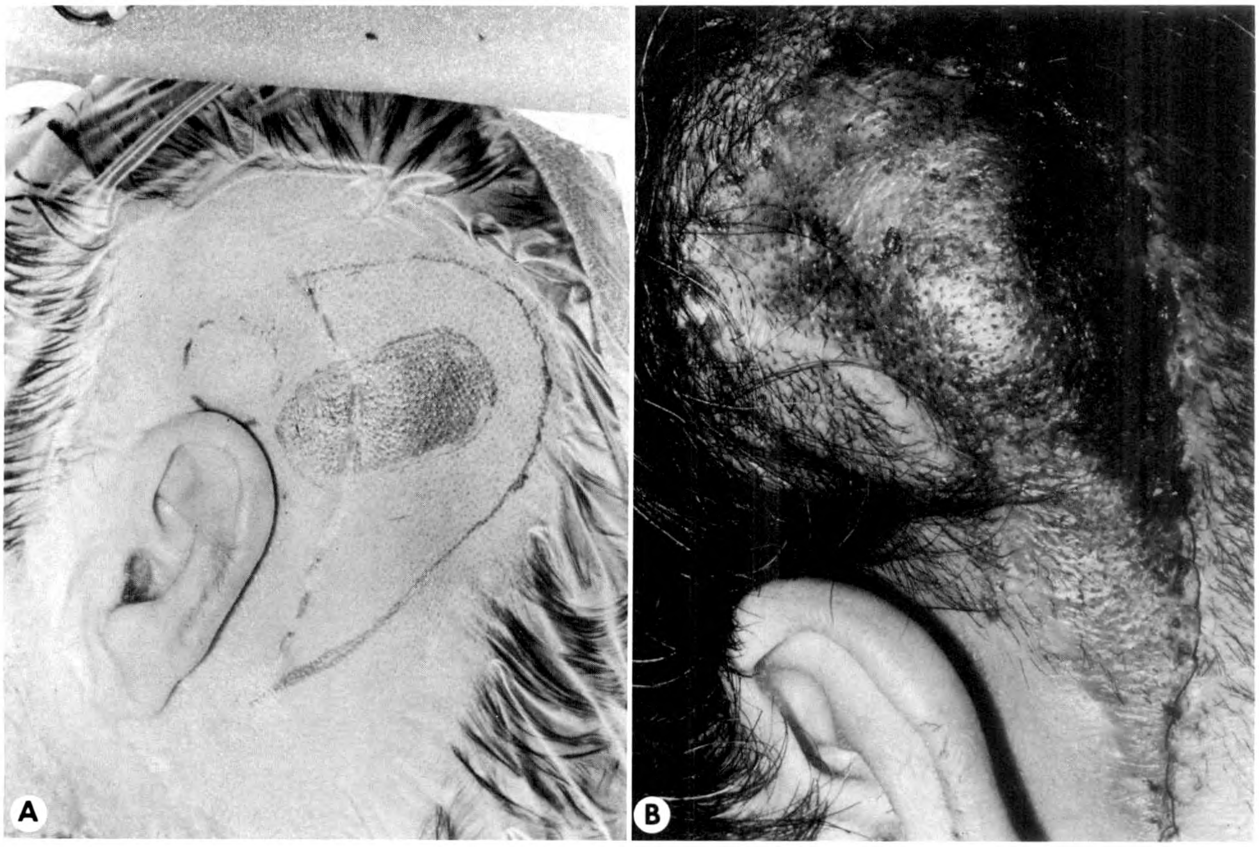

Fig 2. (Case 2) A) Design of flap incision, staggered posterosuperiorly from previous cochlear implant incision. B) Necrosis of skin between new and old incisions on postoperative day 10.

tion, although alopecia remains. He has had no further flap breakdown or changes since.

Cases 3 and 4. These cases represent the extrusion of 0 silk suture material used in securing the internal coil. A 4-year-old girl (case 3) with mild right upper extremity cerebral palsy and congenital binaural deafness underwent left cochlear implantation with a Nucleus 22 multichannel device in June 1988. Four months subsequently, a small area of inflammation and skin breakdown was noted over the internal magnet. The defect was explored in the office and a 0 silk suture removed, resulting in prompt healing within 2 weeks and no further problems since.

A 27-year-old man (case 4) with congenital deafness due to maternal rubella infection underwent insertion of a House/3M single-channel cochlear implant into the right ear in April 1983 after preoperative assessment including an audiogram, aided and unaided, and a CT scan of the temporal bones. Four months postoperatively, after he had used the implant for 3 months, a small abscess overlying the internal magnet was drained and cauterized with silver nitrate. Over the ensuing 3 months, this area developed granulation tissue and continual dehiscence resulting in exposure of the receiver unit despite aggressive local wound care. Finally, a 0 silk suture extruded and was removed from this site, accompanied by prompt healing within a month. Of note, in May 1984 the implant abruptly ceased operating, and revision 2 months later revealed a fractured implant ground wire.

DISCUSSION

In creating a skin flap for cochlear implantation, the portion of the flap overlying the internal coil should be made as thin as possible, usually less than 6 mm^2, to allow optimal transmission and magnet holding. To avoid more widespread thinning of the flap than is necessary, methylene blue is instilled subcutaneously at the anticipated receiver unit location during the flap design. However, excessive thinning of the flap can result in skin breakdown from magnet pressure. In younger children, who have inherently thinner scalp skin, elevation of the postauricular muscle layer in continuity with the skin flap protects the flap, yet keeps it thin enough to transmit well. Proper alignment of the external and internal coils is also important. In case 1, a contributing cause of implant extrusion may have been a failure of the flat receiver device to conform to the skull curvature, so that one edge of the device exerted excessive pressure on the overlying flap.

The design of the flap incision must be tailored to the individual patient, particularly in cases of revision or after prior operation in the region (Fig 3).

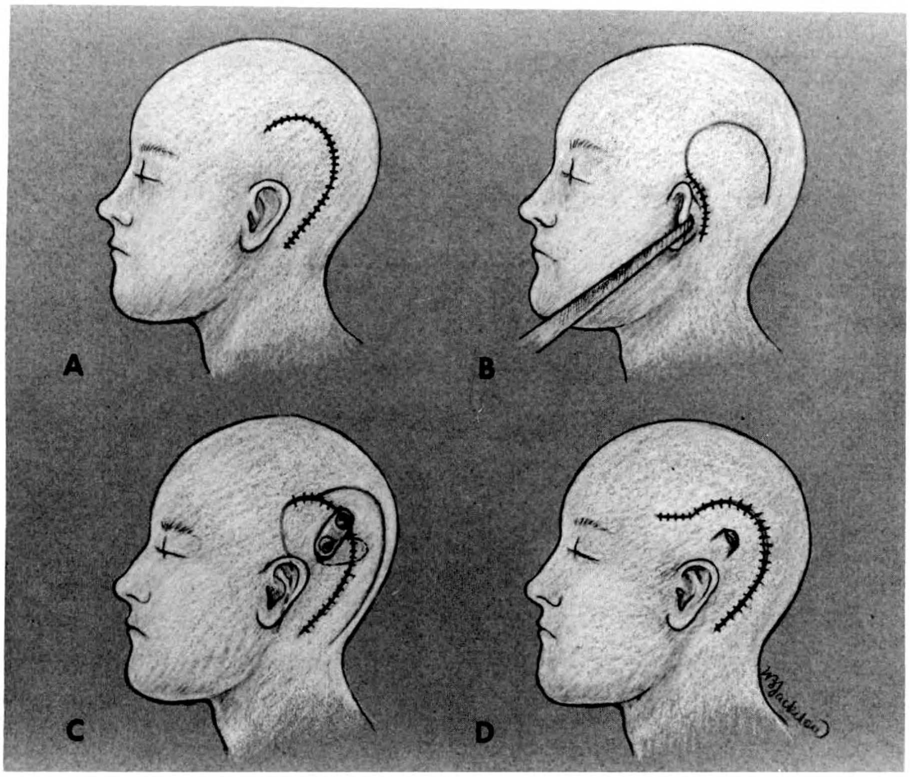

Fig 3. Design of flap incisions. A) Standard anteriorly based flap. B) Inferiorly based flap incorporating previous postauricular incision. C) Inferiorly based flap after prior cochlear implant where larger flap is needed. D) Anterior extension incorporating superior portion of standard incision to raise pericranial flap.

We agree with Harris and Cueva,[1] who reported a case of flap necrosis similar to that in case 2 in a patient who had a postauricular incision for mastoidectomy, that when prior incisions limit the usual superficial temporal artery supply to an anteriorly based flap, it is best to place incisions that take advantage of the occipital artery, and to a lesser extent, the postauricular artery. It is likely that in case 2, skin atrophy from chronic steroid therapy and relative ischemia due to vasculitis were additional adverse factors. The flap should be broad-based to prevent venous congestion. While the recommended minimal distance of the proposed incision line to the edge of the implant varies according to author — from 0.5 cm (Doyle and Pijl[3]) and 1.0 cm (House[4]) to 2.0 cm (Schindler et al[5]) — it is our impression that the incision line migrates toward the implant with scar contracture in the typical anteriorly based flap, and therefore the distance from incision line to implant should be no less than 2.0 cm. Delicate handling of the flap and keeping it moistened are essential, as is the use of a closed suction drainage system to prevent seroma.

The pericranial flap, based anteriorly on the supratrochlear and supraorbital vessels, is used to support the brain and act as a bed for split thickness skin grafting after anterior skull base resection. Even after frequently receiving preoperative radiotherapy to the region, this flap has had a reported overall success rate of 95%.[6] Pericranial flaps can also be based laterally on the temporalis muscle, supplied inferiorly in axial fashion by the two deep temporal arteries that are branches of the internal maxillary artery, and used to reconstruct lateral skull, ear, and face defects.[7-9] The use of a vascularized pericranial flap based upon the temporalis muscle was successful in preventing reextrusion of the internal magnet in the patient in case 1, who appeared to have especially delicate skin, as careful adjustment of magnet strengths and wear duration was necessary even after revision to prevent sustained reactive hyperemia. The pericranial flap is thin, pliable, and durable and can be raised with relative ease as well as with minimal cosmetic and functional morbidity.

Finally, the use of permanent reactive suture in the form of 0 silk caused complications in two cases, in one causing a sustained inflammatory reaction with stitch abscess, granulation tissue, and implant exposure. Instead, 2-0 chromic catgut tied eccentrically to the receiver is recommended to secure implants. It is important to place knots away from the magnetized surface of the receiver unit, on which pressure from the external device could cause localized skin breakdown.

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The Fifth International Symposium on Recent Advances in Otitis Media will be held May 20-23, 1991, at the Sheraton Bal Harbour in Bal Harbour, Florida. For further information, contact David J. Lim, MD, 4331 University Hospitals Clinic, 456 W Tenth Avenue, Columbus, OH 43210; Phone: (614) 293-8103; Fax: (614) 293-5506.

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THE DEAFNESS RESEARCH FOUNDATION OTOLOGICAL RESEARCH FELLOWSHIP FOR THIRD YEAR MEDICAL STUDENTS

The Deafness Research Foundation's Otological Research Fellowship will be sponsored by a department of otolaryngology conducting otological research. Where a unique opportunity exists in a related discipline, the fellowship may be conducted in that discipline while maintaining liaison with the department of otolaryngology. The fellowship would be scheduled as a one-year block of time at the end of the third year of medical school, thus requiring a one-year leave of absence from the medical school curriculum. Applications for 1991 must be received by November 15, 1990. For more information, please contact Walter A. Petryshyn, MD, Medical Director, The Deafness Research Foundation, 9 East 38th Street, New York, NY 10016; (212) 684-6556.

Ann Otol Rhinol Laryngol 99:1990

PERCUTANEOUS PEDESTAL IN COCHLEAR IMPLANTATION

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Direct electrical connection between an external sound-processing device and intracochlear electrodes is accomplished via a percutaneous pedestal. Patient pedestal complaints and experience have been recorded. Pedestal problems have been classified into six classes, with class 0 indicating no problems and the severity of problem increasing in classes 1 through 4. Class 5 indicates pedestal trauma. No class 5 problems were encountered. At 48 months of experience, 53% of patients were class 0 and 26% were class 1. The pedestal experience is detailed in the paper. The percutaneous pedestal has been found to be a well-tolerated, efficient system for information transfer in cochlear implant patients.

KEY WORDS — cochlear implant, percutaneous pedestal.

INTRODUCTION

The efficient transfer of meaningful environmental auditory signals to the auditory nerve of the profoundly deaf patient is a crucial part of cochlear implantation technology. This transfer of information can occur by means of direct wiring through a percutaneous pedestal or by transcutaneous transduction of electrical signals.

The use of a percutaneous pedestal has definite advantages and disadvantages. At the time of surgical implantation when a percutaneous pedestal is used, only electrical wiring is implanted. This allows the testing of electrical impedance at the time of operation for quality control of the unit. The percutaneous pedestal is also minimally affected by thick skin and hair in the area. The sound-processing equipment is all external and can be modified and changed without replacement of the internal device. Since there is no transduction occurring through a percutaneous pedestal, the patients do not experience pickup of extraneous environmental signals such as radar and radio transmissions.

The percutaneous pedestal also has distinct disadvantages. Since the pedestal is a foreign body protruding through the skin, there is the potential problem of bacteria from the external environment causing infection to develop around the pedestal and track down the pedestal to the underlying soft tissue and bone. Cellulitis, mastoiditis, and/or otitis could result. The percutaneous pedestal, which is attached to the underlying skull by securing screws, would have an unknown effect on growing bones if it were to be used in children prior to maturation of the mastoid. The percutaneous pedestal is also exposed to external trauma.

In the early phases of the cochlear implantation project at the University of Utah, various materials were evaluated for possible use as the pedestal. Tissue reactivity was, of course, a major factor considered. It was also decided to select a material that was more fragile than the underlying bone so that direct trauma to the pedestal would cause fracture of the pedestal rather than of the underlying bone. Pyrolyzed carbon was selected as the material fulfilling the considered criteria.

MATERIAL AND METHODS

The implant system used in this study is the Ineraid multichannel cochlear implant, schematically illustrated in Fig 1. The system consists of six monopolar intracochlear electrodes, a promontory electrode, and an indifferent electrode. In the early part of this series, the promontory electrode was implanted in the promontory for experimental testing. More recently, however, the promontory electrode has been implanted in a separate site in the temporalis muscle to be used as a backup indifferent electrode.

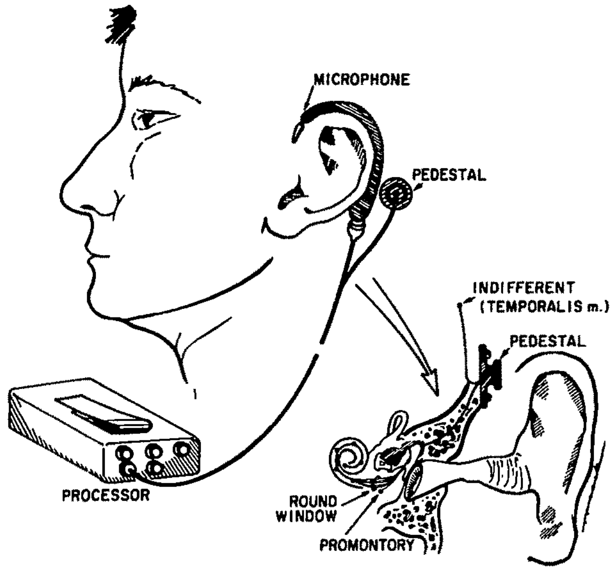

Fig 1. Ineraid multichannel cochlear implant system.

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Presented at the meeting of the American Otological Society, Inc, Palm Beach, Florida, April 28-29, 1990.

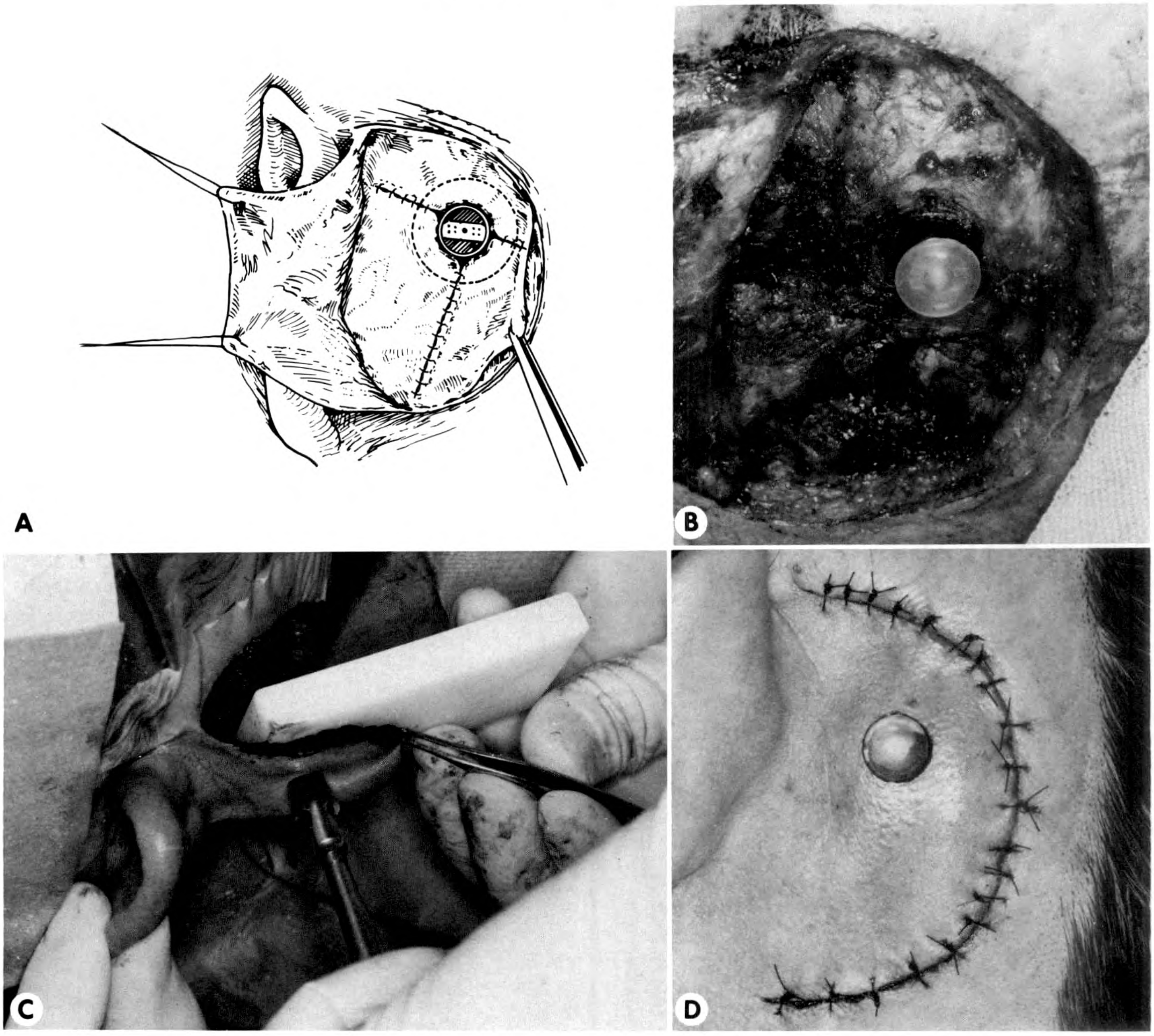

Fig 2. Procedure. A) Trifurcate incision in fascia and periosteum sutured around pedestal. B) Closure of fascia and periosteum around pedestal. C) Penetration of skin flap with custom-sized punch. D) Skin flap seated over pedestal and sutured in position.

All patients in this study were adult, ie, older than 18 years of age, and were postlingually deafened with the exception of the first patient, who was prelingually deafened. Four patients received implants between 1975 and 1977. Forty-two patients received implants between April 1984 and August 1989.

The holding power of the Symbion screw was tested with an Instron model 1000 pull tester equipped with a 100-lb (45 kg) load and an Omega chart recorder that plotted the force versus the distance-pulled curves. The screws were imbedded in 10 different positions of a calf cranium. A pilot hole was drilled without irrigation by use of a sharp twist drill bit and a variable-speed hand drill. The hole was not pretapped. A screw-holding screwdriver fastened the bone screw onto a spacer designed to be pulled by the Instron. The spacer was the same thickness as the pedestal flange (3.18 mm) and made of aluminum.

At the time of cochlear implantation, a depression is made in the mastoid cortex to custom-fit the size of the pedestal. A pedestal marker is used to indicate placement of the securing screw sites.

The pedestal is constructed of pyrolyzed carbon. It is fragile. Care must be taken at the time of implantation that the securing screws are not tightened with too much torque, which can result in fracture of the pedestal. The screws used in securing the early pedestals were a stainless steel screw with a square head provided by Symbion. The final 13 patients in this group had the pedestal secured with a stainless steel screw designed by Synthes with a machine-type head. This change was accomplished to see if the different head design would decrease the incidence of pedestal irritation. It is too early to say if the results with the different screws are significantly different.

TABLE 1. PULL TESTING OF SYMBION BONE SCREW

Pull No.	*Ultimate Force (newtons)*	*Distance Pulled Until Failure (mm)*
1	133	2.8
2	128	2.4
3	145	3.1
4	145	2.5
5	100	2.4
6	171	3.0
7	119	2.3
8	242	2.8
9	111	2.3
10	144	2.8
Mean	144	2.64
SD	40	0.29

The Symbion screw holes were created with a standard mastoid bur. The holes were not pretapped. The Synthes screw holes were created with a straight drill bit and were pretapped. Constant irrigation of the bone occurred as the screw holes were made.

The fascia periosteal layer over the mastoid cortex was elevated as a separate layer either as a trifurcate incision (Fig 2A,B) or as a separate anteriorly or inferiorly based flap with a custom hole secured in the center of the flap. The skin flap was also penetrated with a custom-size skin punch to allow a snug fit around the pedestal (Fig 2C). After the skin flap is sutured down, the pedestal is protected with a plastic cap during the postoperative phase (Fig 2D).

In the postoperative period following removal of the dressing, the patients are instructed to clean the incision line and around the pedestal twice daily with a half-strength hydrogen peroxide solution and apply topical antibiotic ointment. All patients are given prophylactic antibiotics at the time of their operation and for 5 days postoperatively. After healing is complete, patients are allowed to shower and wash their hair normally. Even though they have been instructed not to swim or participate in water sports, many of the patients have elected to do this anyway.

The pedestals were evaluated during routine follow-up audiology visits and at times when patients returned to the clinic for specific pedestal problems. All problems encountered were included in a specific time period.

RESULTS

Testing of the 10 embedded Symbion screws showed ultimate tensile forces of 144 newtons (N) on the average, with a range between 100 N and 242 N (SD = 40 N). The average distance pulled to screw release was 2.64 mm (SD = 0.29 mm). This range deviation would be expected because of different bone characteristics from one pull site to another (Table 1).

From the force-versus-distance plots it was found that the plot was fairly linear right up to failure, at which point the force dropped abruptly to 0. After close examination of the pulled screws, it was obvious that the bone shear failure occurred on the line between the bone screw thread's major diameters, as would be expected.

The pedestal has generally been well tolerated by the patients. Many of the patients do not mention pedestal problems when they return for audiologic follow-up. It has become necessary with many patients to specifically request medical evaluation of pedestal status at the time of audiologic follow-up. Patients with more significant pedestal complaints do request medical evaluation and would have visited the author specifically for pedestal problems at times other than routine audiology follow-up visits.

The first patient receiving the Ineraid cochlear implant with a percutaneous pedestal was operated on by Dr Derald Brackmann in 1975. That patient's pedestal is still in position and has caused no significant problems. Between 1975 and 1977 three additional patients received implants. One of those patients died in 1982 without significant pedestal problems. The second of those three patients was a unilaterally deaf patient who had his cochlear implant performed at the time of other otologic surgery. He participated in extensive experimental testing in the development of the sound-processing strategy. He was subsequently explanted. He also had no significant pedestal problems. The last of that early group of patients was implanted in 1977. He has had several minor infections around the pedestal, which were treated with topical pedestal care and rarely with oral antibiotics. He continues to use his pedestal with his sound processor unit on a daily basis.

Figure 3A is a picture of the first patient who received the implant in 1975. This picture was taken 12 years after his implantation, demonstrating the excellent pedestal tolerance by this patient. Figure 3B indicates a patient in the more recent group. This picture was taken 2 years postimplantation. Figure 3C shows a patient with the ear hook in position.

Forty-two patients were implanted between April 1984 and August 1989. Their pedestal experience was classified into six categories, as follows.

Class 0 — no problems.
Class 1 — minimal pedestal problems consisting of itching, tenderness, and crusting.
Class 2 — mild pedestal complaints consisting of local inflammation or granulation tissue formation requiring topical treatment or oral antibiotics.
Class 3 — moderate pedestal problems requiring systemic antibiotics or surgery.
Class 4 — severe pedestal problems with complica-

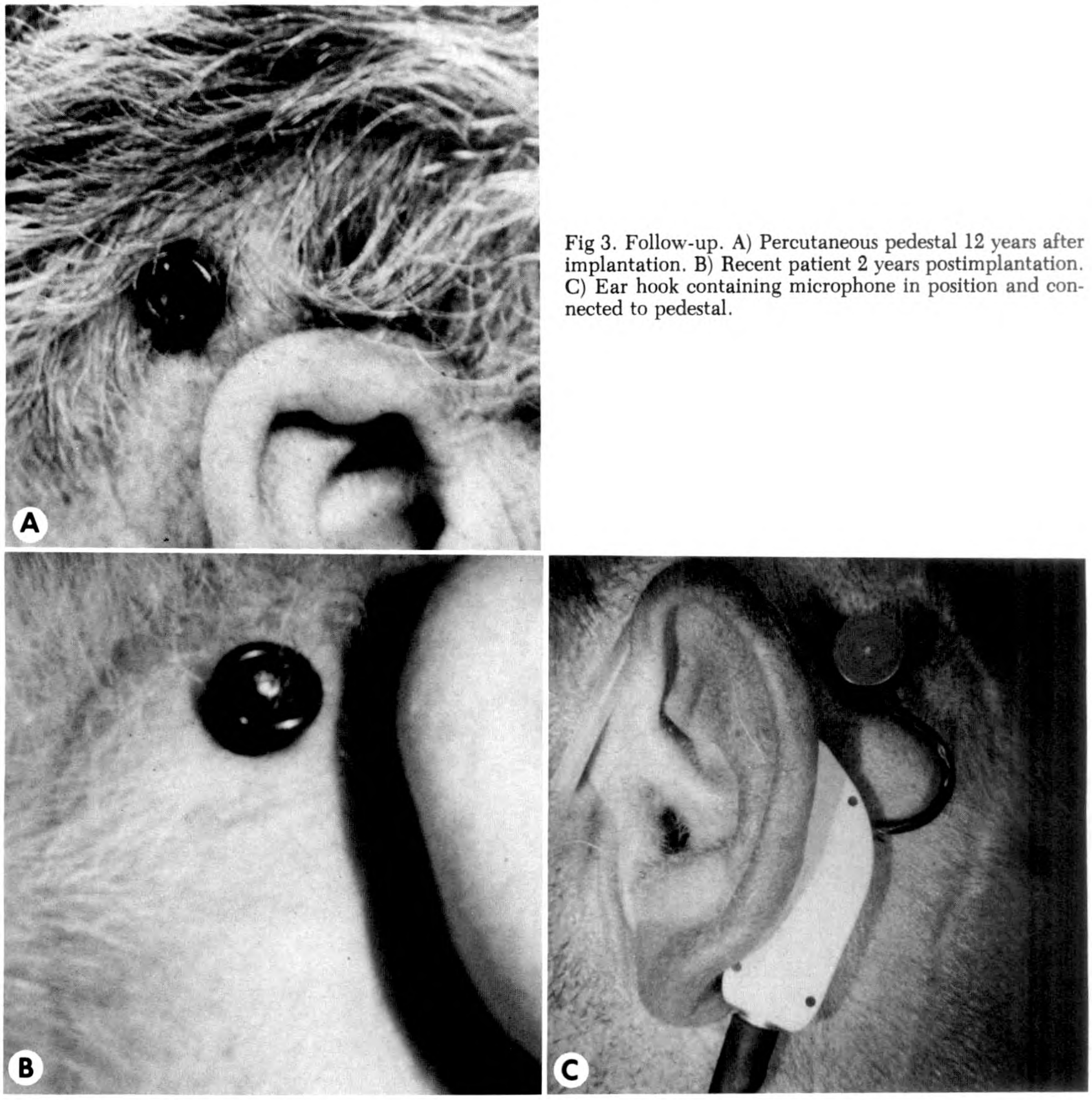

Fig 3. Follow-up. A) Percutaneous pedestal 12 years after implantation. B) Recent patient 2 years postimplantation. C) Ear hook containing microphone in position and connected to pedestal.

tions requiring pedestal removal.

Class 5 — trauma with pedestal fracture requiring removal.

Table 2 shows the results of patient evaluations, which are graphically demonstrated in Fig 4. All patients were evaluated during the first postoperative year. Those results are indicated in the <12-month category. Patients were reevaluated after their pedestals were in place more than 12 months, 24 months, 36 months, and 48 months, respectively.

Two patients experienced class 3 problems at 24 months. The first patient had problems with loosening of several pedestal screws. At 24 months after implantation, this patient was returned to the operating room. New screw holes were created and new securing screws placed. Unfortunately, this patient again developed loosening of the screws. Culture around the pedestal grew out nonhemolytic *Staphylococcus*. The patient was treated with topical care and oral antibiotics. However, the screws continued to loosen and the patient subsequently required removal of his pedestal because of this recurring problem. His is the class 4 pedestal problem indicated in the 48-month group. His initial implantation was in February 1985. His pedestal removal occurred nearly 5 years later.

The second class 3 problem reported at 24 months was in a patient who experienced exposure of the edge of her pedestal. A local skin flap was developed and rotated to provide coverage of the pedestal edge.

Seven additional patients have developed specific irritation around one securing screw. This irritation often results in exposure of that screw. Seven patients have had one screw removed in the clinic. Removal has uniformly reduced the irritation and usually allows skin regrowth covering that portion of the pedestal.

In the latter group of 42 patients (April 1984 to

TABLE 2. PATIENT PEDESTAL EXPERIENCE

	Months Since Implantation				
Class	*<12 (42 Pts)*	*12 (37 Pts)*	*24 (31 Pts)*	*36 (24 Pts)*	*48 (19 Pts)*
0	11 (26%)	9 (24%)	14 (45%)	11 (46%)	10 (53%)
1	19 (45%)	15 (41%)	7 (23%)	6 (25%)	5 (26%)
2	12 (29%)	13 (35%)	8 (26%)	7 (29%)	3 (16%)
3	0 (0%)	0 (0%)	2 (6%)	0 (0%)	0 (0%)
4	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (5%)
5	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

See text for definition of classes.

August 1989), 2 patients have had pedestal removal for nonpedestal problems. In 1 of these patients, at the time of initial implantation, the cochlea would not accept the entire electrode bundle, so 5 months later that system was removed and the opposite ear was implanted. In a second patient, the electrode system failed to perform to expectation, so 9 months after initial implantation his implant was replaced in the same ear. At the time of the repeat operation, both of these pedestals were found to be firmly attached to the temporal bone. Dense fibrous tissue had grown around the pedestal base and through the unused screw holes. (The pedestal has eight holes for screw fixation, but only four or five screws are placed.) New bone had formed in the groove beneath the pedestal created for the electrode bundle. There was no evidence of active infection around either pedestal, and no unusual postoperative pedestal problems had occurred in either of these patients to the time of their removal operation.

No patient has experienced mastoiditis, otitis media, or meningitis in this series. Infections that have developed have remained localized to the tissues immediately surrounding the pedestals. Small granulomas occasionally form around the pedestal site at the time of local infections. These have been successfully managed with silver nitrate cautery.

DISCUSSION

Percutaneous pedestals have been used and well tolerated for bone-anchored hearing aids. Holgers et al[1] have reported excellent tolerance of these devices. They indicated a failure rate of 0.07% per month, which they stated is comparable to the failure rate of implanted cardiac pacemaker devices.

That group has also reported infection problems developing around such implants.[2] Their implant material was titanium. These implants have also been used for anchoring cosmetic prostheses.[3] Irradiated patients have a higher failure rate with percutaneous prostheses than do nonirradiated patients.[4]

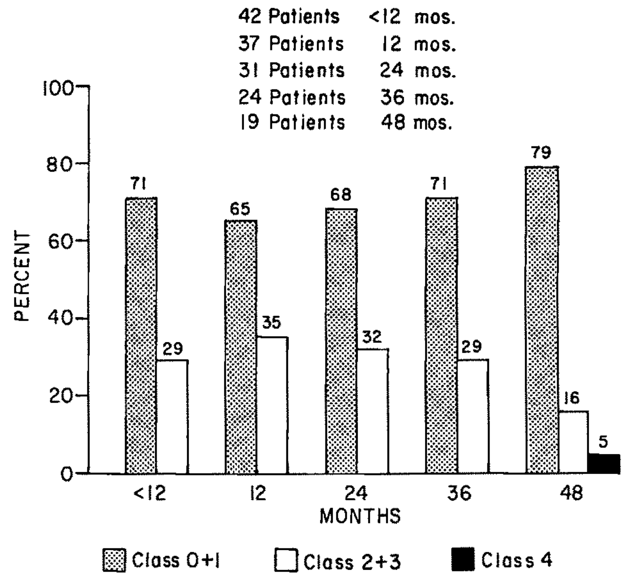

Fig 4. Pedestal experience of 42 patients implanted between April 1984 and August 1989.

The percutaneous pedestal has been found to be well tolerated in the patient group reported in this paper. As time from implantation increases, a higher percentage of the patients are found in the 0 classification group (Table 2).

SUMMARY

The percutaneous pedestal is used to allow direct wiring contact between the electrical signal from the sound processor and the stimulating intracochlear electrodes. This system has the distinct advantages of direct wiring, little effect from thick skin and hair, no pickup of extraneous environmental signals, and external placement of all sound-processing hardware.

The potential disadvantage of external infection invading a percutaneous foreign body tract does exist with this pedestal system. The experience reported in this paper indicates the percutaneous pedestal is well tolerated by a vast (95%) majority of patients, with an acceptably low complication rate.

ACKNOWLEDGMENT — The author thanks Patrick Campbell, who performed the screw pull testing studies.

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FURTHER STUDIES ON THE EFFECTS OF MAGNETIC RESONANCE IMAGING FIELDS ON MIDDLE EAR IMPLANTS

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We investigated the effects of magnetic resonance imaging (MRI) fields on 21 stapedectomy prostheses and other middle ear implants and two different receiver-stimulator modules from 22-channel cochlear implants. None of the middle ear implants was displaced by the magnetic field, except for one platinum-stainless steel stapedectomy piston. Magnetism was not induced in any of the middle ear implants subjected to prolonged exposure in the MRI scanner. We conclude that MRI could pose a hazard to patients who have had stapedectomy using certain platinum-stainless steel piston prostheses and to patients with cochlear implants. Magnetic resonance imaging should pose no hazard to patients who have had the other middle ear implants reported on in this and our previous investigation.

KEY WORDS — magnetic resonance imaging, middle ear implants, stapedectomy prostheses.

INTRODUCTION

During the past decade, magnetic resonance imaging (MRI) has evolved into an indispensable diagnostic imaging modality for the head and neck and all other anatomic regions. The combination of excellent soft tissue visualization without the use of ionizing radiation has resulted in the rapid and widespread clinical application of MRI. To produce their images, MRI scanners generate powerful static magnetic fields; weak, rapidly varying, gradient magnetic fields; and radio frequency pulses. The safety of these electromagnetic fields has been investigated in more than 30 recent studies that fail to disclose any health risks associated with the contemporary operating levels of MRI scanners.[1]

Patients who need MRI may have had a middle ear or cochlear implant. Potential hazards must be considered to patients with these implants. The implants may be heated to harmful levels or displaced by the effects of the electromagnetic fields of the MRI scanner. Additionally, cochlear implants are subject to radio frequency interference that could be induced into their receiver coils and transmitted via their electrodes to the auditory pathway with harmful effects.[2] Temperature elevations induced by MRI of metallic implants much larger than those used in the ear appear to be negligible.[3-5] Displacement of ferromagnetic middle ear implants remains a hazard, and some authors consider stapedectomy prostheses a relative contraindication to MRI unless they are known not to be ferromagnetic.[6]

TABLE 1. STAPES PROSTHESES STUDIED PREVIOUSLY

- Xomed stapes prosthesis, Robinson style, 4 x 0.8 mm
- Richards McGee piston, 4 x 0.8 mm
- Richards McGee piston, 5 x 0.6 mm
- Richards Schuknecht Teflon-wire piston, 4 x 0.6 mm
- Richards Plastipore piston with Armstrong-style platinum ribbon loop, 4 x 0.8 mm
- Richards trapeze platinum ribbon loop, 4 x 4.75 mm
- Richards House-type wire loop, 4.25 mm

Information from reference 7.

Our initial study of the effects of MRI fields on stapedectomy prostheses showed no displacement of the seven different types of widely used implants (Table 1[7]) that were subjected to the magnetic fields of a 1.5-T imaging unit.[7] Subsequent published studies also reported the lack of MRI displacement of 15 middle ear prostheses studied ex vivo.[8-10] A compilation of the prostheses reported in these studies is shown in Table 2.[8-10]

To expand our previous investigation to metallic middle ear implants not studied previously, and to study nonmetallic implants for displacement due to

TABLE 2. MIDDLE EAR IMPLANTS AND MATERIALS TESTED FOR DEFLECTION BY MRI UNITS

- Treace stainless steel total ossicular replacement prosthesis, 0.6 x 8 mm
- Richards shepherd's crook platinum ribbon piston, 1 mm
- Richards McGee stainless steel piston, 0.6 x 4.25 mm
- Otomed House-type stainless steel wire, 5.75 mm
- Otomed House-type stainless steel prosthesis, 4.5 mm
- Xomed Robinson stainless steel prosthesis, 4.5 mm
- Richards Schuknecht Teflon-wire prosthesis
- Richards Gelfoam-wire prosthesis
- Richards Shea stainless steel and Teflon prosthesis
- Richards House-type incus prosthesis
- Richards Plastipore piston with wire loop
- Richards Reuter drain tube
- Richards Cody tack
- Richards Armstrong model of Schuknecht Gelfoam-wire prosthesis, 4.5 mm

Information from references 8-10.

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TABLE 3. MIDDLE EAR AND COCHLEAR IMPLANTS STUDIED

Description	*Material*
Shea cup piston	Teflon
Shea malleus attachment piston	Teflon
Richards Teflon piston	Teflon
Sheehy incus strut	Stainless steel
House-type wire loop	Stainless steel
McGee piston, 0.6-mm diameter	Stainless steel
McGee piston, 0.8-mm diameter	Stainless steel
Tantalum wire loop	Tantalum
Schuknecht malleus attachment piston	Teflon–stainless steel
Schuknecht piston, 0.6-mm diameter	Teflon–stainless steel
Schuknecht piston, 0.8-mm diameter	Teflon–stainless steel
Fisch piston, 0.4 mm	Teflon–stainless steel
Scheer piston	Teflon–stainless steel
Richards bucket-handle prosthesis	Teflon–stainless steel
Silverstein malleus clip ventilation tube	Teflon–stainless steel
Shea platinum Teflon cup piston	Teflon-platinum
Richards platinum Teflon piston, 0.6-mm diameter	Teflon-platinum
Richards platinum Teflon piston, 0.8-mm diameter	Teflon-platinum
Plastipore piston with Armstrong-style platinum ribbon	Porous polyethylene–platinum
McGee platinum–stainless steel piston	Stainless steel–platinum with Teflon connections
Total ossicular replacement prosthesis	Porous polyethylene
Receiver-stimulator module, Nucleus 22-channel cochlear implant	Titanium and ceramic case in silicone elastomer capsule; platinum coil, platinum, ceramic, and silicone rubber interconnection assembly, fastened with titanium screw
Electrode array	Platinum electrode rings molded with silicone rubber elastomer carrier; Teflon-insulated platinum-iridium wires
Receiver-stimulator module, Nucleus Mini 22-channel cochlear implant	Titanium and ceramic case in silicone elastomer capsule; platinum coil; magnet
Electrode array	Teflon-insulated platinum-iridium wire; platinum electrode rings molded with silicone elastomer carrier

possible occult ferromagnetic contaminants, we extended our initial research to include these implants and to investigate two widely used 22-channel cochlear implant receiver-stimulator modules. Additionally, we investigated the possibility that exposure to the strong magnetic fields of MRI units could induce ferromagnetism into middle ear metallic implants that did not exhibit magnetic properties prior to MRI exposure.

MATERIALS AND METHODS

The prostheses used in this study are listed in Table 3. All middle ear and cochlear implants were new and supplied by their manufacturers (Richards Medical Company, Memphis, Tenn, and Cochlear Corporation, Englewood, Colo, respectively). Each of the middle ear prostheses was placed on a millimeter scale in a covered plastic Petri dish (Fig 1) that was placed on the transport platform of the MRI unit (General Electric Signa, 1.5 T, operated at maximum output of 15,000 G). Movement of the Petri dish was smoothly controlled by the transport platform into and out of the MRI unit's core. Three observers using magnifying glasses noted and recorded any displacement of the prostheses along or off of the millimeter scale. After a passage into and out of the MRI unit, each prosthesis was rotated 90° and the process was repeated.

Those middle ear implants that showed no evident ferromagnetism by lack of detectable movement in the MRI unit's field were then left in the unit's core for 90 hours — far longer than in any single or cumulative MRI studies likely to be encountered in clinical practice. These implants were tested for induced magnetism by exposing them to a powerful electromagnet upon their removal from the MRI unit.

The cochlear implant receiver-stimulator modules were hand-held during preliminary exposure to the MRI unit core. If gross displacement of these units was noted, the receiver and electrode arrays were then tested separately. If no gross displacement was noted, testing was repeated with the implant on a millimeter scale and three observers noting any displacement.

RESULTS

No middle ear prosthesis listed in Table 3 was displaced during exposure to the magnetic field of the MRI unit except for the McGee platinum–stainless steel stapedectomy piston. This implant was impelled rapidly and suddenly against the Petri dish edge when it was brought within 1 m of the MRI unit's opening. The other middle ear prostheses that showed no displacement and were then exposed to the magnetic field at the core of the MRI unit for 90 hours did not show any induced magnetism and were not displaced by a powerful electromagnet after their prolonged exposure.

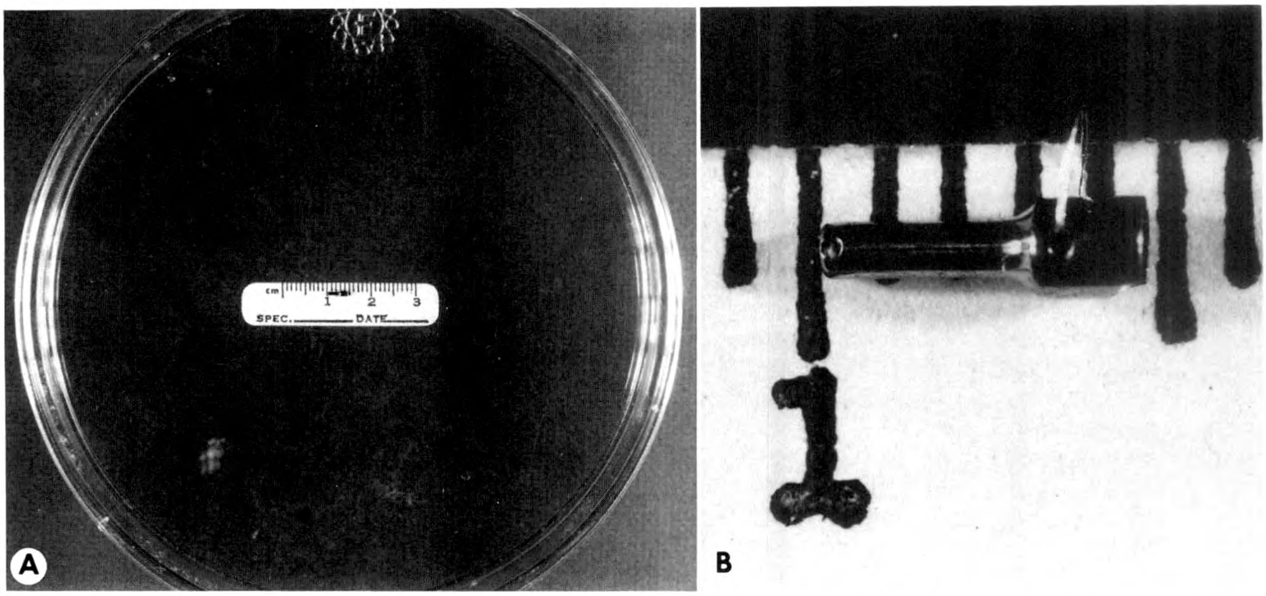


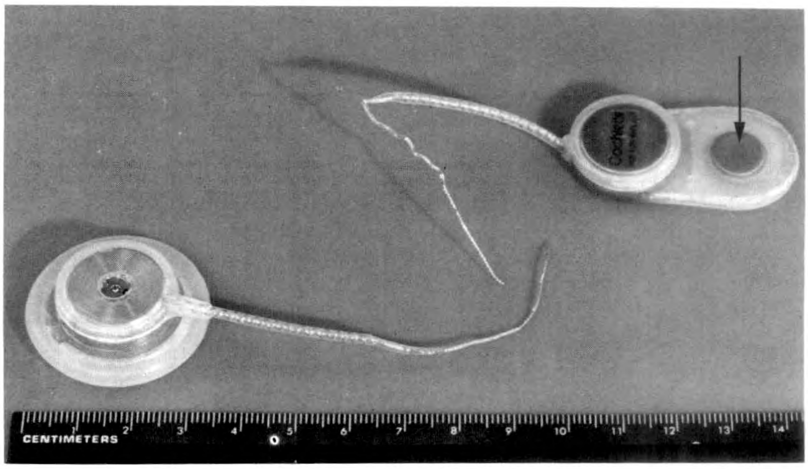
Fig 1. Metallic stapedectomy prosthesis for testing in magnetic resonance imaging field. A) Plastic Petri dish with millimeter scale and prosthesis. B) Magnified view of scale and prosthesis as seen by observers.

The standard design Nucleus 22-channel cochlear implant receiver-stimulator module and electrode array showed no displacement by the magnetic field of the MRI unit. The Nucleus Mini 22-channel cochlear implant receiver-stimulator module contains a permanent magnet (Fig 2) and was strongly attracted to the magnetic field when hand-held within 1 m of the MRI unit. The electrode array of this unit did not seem to be displaced by the magnetic field independent of the forces exerted on the receiver-stimulator module.

DISCUSSION

We were surprised that the McGee platinum–stainless steel piston was affected by the magnetic field, since this and our initial study showed no displacement of the same prosthesis design (from the same manufacturer) made entirely of stainless steel. Both types of prostheses have stainless steel pistons, but one is configured entirely of stainless steel and the other has a platinum ribbon for attachment to the incus. Platinum itself is not ferromagnetic and should not be displaced by magnetic fields. Yet the original all–stainless steel McGee piston reported in our initial study and both stainless steel McGee pistons tested in this study showed no displacement in the MRI unit. Communication with the manufacturer resulted in their sending us other McGee platinum–stainless steel pistons bearing different manufacturer's lot numbers. Some of these were displaced by the magnetic field, but others were not. The manufacturer conducted an internal investigation and found that some lot numbers of these prostheses were made of one type of stainless steel (316L) that is not ferromagnetic, and the others were made of another type of stainless steel (17Cr-4Ni) that is ferromagnetic. Fortunately, the latter prostheses were manufactured in a relatively small quantity and only after mid-1987. The Richards Medical Company (now Smith & Nephew Richards, Inc) instituted a recall program for all McGee platinum–stainless steel piston prostheses. Those that were returned and had been manufactured before

Fig 2. Standard design (left) and Mini design of Nucleus 22-channel cochlear implant receiver-stimulator modules. Mini unit contains permanent magnet (arrow) that caused it to be displaced by magnetic resonance imaging field.



1987 showed no ferromagnetic properties. The manufacturer contacted the hospitals and physicians to whom ferromagnetic implants were distributed, and when patients were identified who had received them, they were issued cards warning them not to have MRI studies.

Most metallic surgical implants are made of 316L stainless steel, and even large spine implants constructed of this material have not been displaced by MRI fields.[3] All of the metallic middle ear implants we tested were made of 316L stainless steel except for the piston portion of the McGee platinum–stainless steel piston, which in some instances had been made from 17Cr-4Ni stainless steel. The 316L stainless steel is an austenitic stainless steel with a nickel content of 10% to 14% and with each atom in its crystal structure belonging to more than one other crystal. This configuration causes a net electron balancing system with no electron-dense or electron-poor areas. Electron-balanced materials will not react electromagnetically. In general, austenitic stainless steels with a high nickel content are paramagnetic and do not react in magnetic fields. In contrast, the 17Cr-4Ni stainless steel is a martensitic steel that has a nickel content of 4% and a crystal structure with electron-dense and electron-poor areas. This imbalance produces ferromagnetic characteristics in the metal, enabling it to react in a magnetic field and in some instances to display permanent magnetic properties.

Hundreds of metallic surgical implants of all kinds and hundreds of patients with these implants have been studied in the magnetic fields of MRI units.[5,11,12] Most implants are not affected by the magnetic field to the extent of producing a biologic hazard, but there are notable exceptions. Aneurysm clips have been shown to develop sufficient torque when placed within the magnetic fields of an MRI unit to result in injury.[11,12] Patients with cardiac pacemakers or other electrical stimulating devices should not have MRI examinations, since electrical currents may be induced into the electrodes and the stimulator mode may be changed by the magnetic field. Our study has disclosed potential hazard from MRI displacement of ferromagnetic middle ear implants. Our findings with cochlear implants reinforce the conclusions of other investigators who agree that patients with cochlear implants should not have MRI studies.[1]

Since MRI studies are now firmly established as necessary in many disorders, we recommend the adoption of the following measures to increase the relative safety of this imaging technique in patients with metallic ear implants.

1. All implants should be manufactured of materials that will not exhibit ferromagnetic properties.
2. Implants should be tested by their manufacturers and certified to be nonferromagnetic.
3. Surgeons should record the lot numbers of all implants, as well as their type and size, in the operative record. This information could be invaluable in the event that an implant is found to be ferromagnetic (or is recalled for any reason).
4. Studies should be done on cochlear implants to determine if the receiver-stimulator modules are actually displaced by MRI fields when they are secured firmly in situ.
5. Studies should be done on cochlear implants to determine if damaging or interfering electrical currents are induced into the electrode array by the electromagnetic fields produced by MRI units.

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VESTIBULAR RECRUITMENT IN MENIERE'S DISEASE

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The aim of this study was to search for vestibular recruitment in a sample of patients with Meniere's disease. Recruitment was defined as an abnormal growth of response with increasing stimulus intensity. Twenty-nine patients were tested with sinusoidal rotation of three different magnitudes at four different frequencies. We also searched for auditory recruitment in each patient via tests of auditory brain stem responses, acoustic reflexes, and loudness balance and discomfort level. Analysis of vestibular responses indicated, on average, a linear relationship between stimulus magnitude and response magnitude, ie, doubling the stimulus magnitude resulted in twice the response magnitude. Meniere's patients did not yield results significantly different (although they were more variable) from those of the normal subjects. The vestibular responses of patients with auditory recruitment did not differ systematically from those of patients without auditory recruitment. We conclude that vestibular recruitment, if it exists in patients with Meniere's disease, is not demonstrated by sinusoidal rotational testing.

KEY WORDS — Meniere's disease, rotational testing, vestibular recruitment.

INTRODUCTION

The aim of this study was to search for vestibular recruitment, operationally defined as an abnormal growth of response with increasing stimulus intensity, by use of sinusoidal rotational stimulation. Previous efforts to establish the existence of vestibular recruitment have employed either caloric stimuli of various temperatures[1,2] and durations[3] or rotation of various magnitudes.[4-6] Results of these studies have suggested that some patients manifest signs of vestibular recruitment. However, a search for vestibular recruitment is not part of routine vestibular laboratory evaluations. The lack of popularity of vestibular recruitment evaluation may be based on the unpleasantness of multiple caloric irrigations or the technical difficulty of recording reliable eye movement responses to graded rotational velocity trapezoids. (That is, low-amplitude trapezoids produce minimal eye movements, whereas high-amplitude trapezoids produce excessive rotational chair velocities after only a few seconds of testing.)

To search for vestibular recruitment, we chose sinusoidal rotational stimulation because multiple frequency-magnitude combinations are tolerated well and the testing is available in many vestibular diagnostic centers. We chose to study patients with Meniere's disease because 1) vestibular recruitment has been suggested to occur in this condition,[2,6-8] 2) both the auditory and the vestibular apparatuses are involved in this disorder, and 3) patients with Meniere's disease often have auditory recruitment.

METHODS

CLINICAL SUBJECTS

Patients were selected from the otologic practice of University Otolaryngology–Head and Neck Surgery, Inc, at Eye and Ear Institute of Pittsburgh. Criteria for inclusion were those of the American Academy of Otolaryngology–Head and Neck Surgery, Inc, for a diagnosis of Meniere's disease.[9] The sample acquired consisted of 29 patients ranging in age from 30 to 69 years (mean, 54 years; 8 men and 21 women). None of the patients tested was undergoing an acute exacerbation at the time of testing or had suffered an exacerbation within a month prior to testing.

NORMAL SUBJECTS

The control subject group consisted of 14 persons (5 men and 9 women) ranging in age from 34 to 71 years (mean, 53 years). Criteria for inclusion were absence of history of previous otologic or neurologic disease and no ongoing or prior complaints of dizziness, dysequilibrium, hearing loss, or tinnitus. Exclusionary criteria included a hearing loss greater than 25 dB in the range of 500 to 4,000 Hz, a significantly (>24%) reduced vestibular response, and significant (>29%) directional preponderance on alternate binaural bithermal caloric testing.

AUDIOMETRIC TESTING

Each patient underwent routine audiologic testing including pure tone and speech audiometry and tympanometry. Four special tests were also administered: acoustic reflex threshold test, assessment of loudness discomfort level, alternate binaural loudness balance, and examination of the auditory brain stem response with click stimulation. For each of these tests a judgment regarding the presence or absence of auditory recruitment was rendered according to the following criteria.

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Acoustic Reflex Threshold. Auditory recruitment was judged to be present if reflexes (contralateral) were present at reduced sensation levels. The criterion levels adopted were Priede and Coles's[10] 50th percentile diagnostic data, as opposed to the use of a fixed sensation level. The fixed-level approach is likely to be too strict in cases of mild hearing loss and too liberal in cases of severe loss, whereas the criteria of Priede and Coles effectively adjust for hearing loss. The test frequencies were 0.5, 1.0, and 2.0 kHz. Recruitment was considered probable if the findings were positive for two of the three test frequencies.

Loudness Discomfort Level. Auditory recruitment was judged to be present if loudness discomfort was measured at reduced sensation levels, also according to data of Priede and Coles.[10] However, the stimuli used were spondees presented via monitored live voice and referenced to the speech reception threshold (rather than a 1-kHz tone).

Alternate Binaural Loudness Balance. Auditory recruitment was judged to be present if full recruitment was measured at one or more frequencies, as defined by balance at equal hearing levels within 10 dB. Subjects were required to have an interaural difference of ≥15 dB at one or more audiometric frequencies from 0.5 to 4.0 kHz. Only 19 subjects met this requirement, and of these, 14 presented with ≥40 dB difference at one or more test frequencies. The test procedure involved adjustment of the stimulus in 10-dB intervals fixed in the poorer ear and bracketing of the level in 5-dB steps in the better ear to achieve a balance by use of the method of limits (an adaptation of the method of Jerger[11]).

Auditory Brain Stem Response. Auditory recruitment was judged to be present, in subjects with 4-kHz pure tone thresholds of ≥25 dB hearing level, if wave V latencies were within 2 SD of mean values of our clinical norms at 70 and 90 dB normal hearing level. In subjects with high-frequency hearing losses ≥50 dB at 4 kHz, auditory recruitment was judged to be present if there was clear convergence of the two-point latency-intensity function toward the normal function, such that at 90 dB normal hearing level the wave V latency fell within 2 SD of the normative mean.

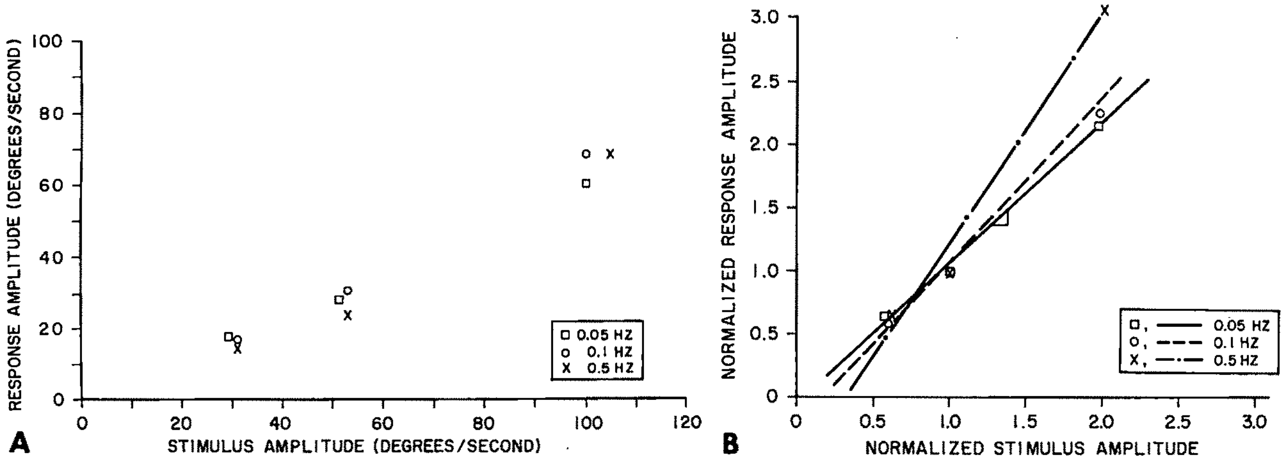
It is important to note that only two of the above procedures are legitimately viewed as tests of loudness recruitment per se, ie, alternate binaural loudness balance and loudness discomfort level. However, the acoustic reflex threshold test and auditory brain stem response to click stimulation are assumed to reflect auditory recruitment or recruitmentlike phenomena wherein normal or near-normal responsiveness is achieved at reduced sensation levels of stimulation. We chose to use multiple tests here because of the interaural asymmetry required for use of the alternate binaural loudness balance test and because it and loudness discomfort level are subjective measures. A "recruitment present" judgment required auditory recruitment on at least two of the four tests.

VESTIBULAR TESTING

Prior to performance of the vestibular recruitment test battery, each patient and normal subject was tested with an ocular motor screening battery. Testing was performed with electro-oculography by use of silver–silver chloride electrodes affixed bitemporally to record horizontal eye movements. Electrodes were placed above and below one eye for recording vertical movements. The electro-oculographic signal was fed to a DC-coupled signal amplifier with a high-frequency cutoff of 40 Hz. Testing included a search for nystagmus with fixation in the primary position and with horizontal and vertical gaze deviation. In addition, each subject and patient underwent testing of horizontal voluntary saccades and pursuit tracking by use of a laser-generated target that moved under computer control. The results of ocular motor screening batteries were within normal limits in all clinical and normal subjects. Results of alternate binaural bithermal caloric testing were available for 20 of the patients. The other 9 patients were not tested with caloric irrigation at our facility.

Earth vertical axis rotational testing was performed with a 28-foot-pound turntable. Rotational testing was performed at 0.05, 0.1, and 0.5 Hz with a peak velocity of 30°, 50°, and 100° per second at each frequency. The eye movement response to sinusoidal rotation was monitored with electro-oculography and recorded on both a chart recorder and a frequency modulation tape recorder for off-line computer analysis. The eye-position-versus-time data were analyzed by an algorithm that detected and removed fast components of vestibular-induced nystagmus to yield cumulative slow component eye velocity.[12] The slow component eye velocity data were used to compute peak slow component eye velocity, phase, and DC shift of the vestibular response by use of a cycle-by-cycle least-squares-fit algorithm. Averages of 3, 5, and 4 cycles of data were used at 0.05, 0.1, and 0.5 Hz, respectively. A wild-point editing procedure was used to discard individual cycles for each patient for whom peak slow component eye velocity or phase estimates were outside the mean ± 3 SD for that patient's response at each combination of stimulus frequency and amplitude.

At each frequency, growth of vestibular response was assessed by use of the peak slow component eye velocity at each of the three stimulus magnitudes. The Figure, A, illustrates representative data from a single patient's responses at each of the three frequencies used. To compute the growth of vestibular response, peak slow component eye velocity was normalized on the basis of the response to the 50°/s



Method of quantitating growth of vestibular response. A) Representative data from patient with Meniere's disease. Peak slow component eye velocity response versus peak stimulus velocity for rotational stimulation at 0.05, 0.1, and 0.5 Hz. Note that as stimulus velocity increases, response amplitude (peak slow component velocity) also increases. B) Same data as in A but normalized about 50°/s peak velocity stimulus and response. Least-squares straight line is drawn through data. Slope of this line was taken as measure of growth of vestibular response.

peak velocity stimulus. The Figure, B, shows the normalized growth of response data based on the responses depicted in A. Note that by definition, the normalized stimulus amplitude and the normalized response amplitude for the 50°/s peak velocity stimulus are both unity. Once the data were normalized, we computed a least-squares, straight-line fit for the vestibular response at each frequency. The slope of this line was taken as a measure of the growth of vestibular response, ie, a slope significantly greater than unity suggests an abnormally high growth of response, defined by us as vestibular recruitment.

Because of the substantial variability of the data, we conducted a nonparametric analysis using Fisher's exact probability test. This categorically based analysis, which involved combining data across test frequencies, was used to compare the incidence of vestibular recruitment in the normal group versus that in the patient sample and subgroups thereof.

Because previous investigators have suggested that changes in asymmetry with increasing stimulus intensity may be a sign of vestibular recruitment,[13] we evaluated DC shift of the rotation response as a function of stimulus intensity. We also evaluated rotation response phase as a function of stimulus magnitude at 0.05 and 0.1 Hz as another possible indication of dependence of response on stimulus magnitude.

RESULTS

Table 1 shows the growth of vestibular response data for both the patient and the normal subject populations, indicating mean ± 1 SD. The sizeable SD values reflect the substantial variability of the data, especially those of the clinical subjects. Also of note is that the SD for the patient data increased with increasing frequency, while those for normal subjects decreased with increasing frequency. Nevertheless, on average, the growth of vestibular response is nearly unity at each of the three frequencies tested, regardless of subject group. This finding indicates that the vestibulo-ocular reflex is acting as a linear system for both the clinical and normal subjects; ie, doubling the stimulus leads to twice the response.

Considering the greater variability of the data from the clinical sample, we examined the data from selected subgroups of the patients to explore the possibility that the patient sample was not homogeneous. First, the growth of vestibular response data from those patients judged to have auditory recruitment (see Methods) was examined (Table 1). We found no obvious difference between the patient and the normal subject samples. The growth-of-response data from those patients with a reduced vestibular response (greater than 24% on caloric testing) were also averaged separately. Again, we found no obvious difference between results from the clinical versus the normal subjects.

There was no alteration in rotation response phase as a function of stimulus intensity at any of

TABLE 1. NORMALIZED GROWTH OF VESTIBULAR RESPONSE (MEAN ± SD)

Group	*0.05 Hz*	*0.1 Hz*	*0.5 Hz*
All patients (n = 29)	0.90±0.40	0.98±0.68	1.19±0.82
Patients with auditory recruitment (n = 20)	0.98±0.40	0.90±0.48	1.09±0.61
Patients with full ABLB recruitment (n = 14)	0.86±0.41	0.99±0.42	1.16±0.63
Super-recruiters (n = 7)	0.71±0.38	1.11±0.45	1.19±0.76
Patients with unilateral RVR (n = 10)	0.82±0.41	0.85±0.61	1.13±0.79
Normal subjects (n = 14)	0.92±0.33	0.86±0.32	0.79±0.18

ABLB — alternate binaural loudness balance, RVR — reduced vestibular response.

TABLE 2. NUMBER OF PERSONS JUDGED TO HAVE VESTIBULAR RECRUITMENT

Group	*Vestibular Recruitment*	*No Vestibular Recruitment*
All patients (n = 29)	8	21
Patients with auditory recruitment (n = 20)	5	15
Patients with full ABLB recruitment (n = 14)	4	10
Super-recruiters (n = 7)	1	6
Patients with unilateral RVR (n = 10)	2	8
Normal subjects (n = 14)	2	12

ABLB — alternate binaural loudness balance, RVR — reduced vestibular response.

the three frequencies studied. That is, on average, phase neither increased nor decreased as stimulus amplitude increased, either in the normal subject group or in the patient group. We obtained a similar result for rotation response asymmetry as a function of stimulus intensity. Thus, no increase or decrease in DC shift was observed as stimulus intensity increased.

In an effort to identify patients with possible vestibular recruitment on a case-by-case basis, each subject was judged individually regarding the presence of vestibular recruitment. Persons were judged to have vestibular recruitment if 1) their growth of response value at one or more frequencies exceeded the mean + 2 SD, or 2) values at two or more frequencies exceeded the mean + 1 SD, and if both conditions were satisfied, no value was less than the mean − 1 SD at any frequency (re: normal subject data). Table 2 indicates the number of persons judged to have vestibular recruitment by use of these criteria in both the normal and patient groups. The patient population was again subdivided on the basis of their auditory and caloric test results, in this case into four (nonexclusive) groups. Auditory recruiters were patients with positive findings on two or more "auditory recruitment" tests (see Methods); alternate binaural loudness balance recruiters were patients who demonstrated full loudness recruitment (at least at one test frequency on the alternate binaural loudness balance test); super auditory recruiters were patients with positive findings on all "auditory recruitment" tests; and reduced vestibular response patients were those who had a reduced vestibular response of greater than 24% on caloric testing. Table 2 gives the numbers of patients in these subgroups who were or were not judged to have vestibular recruitment. Statistical analysis (Fisher's exact probability test) revealed that the presence of vestibular recruitment did not occur in the clinical group or subgroups with frequencies beyond the chance level ($p < .05$). The slightly higher incidence of vestibular recruitment for the clinical subjects (all groups) presumably reflects simply the greater variability of the clinical data.

DISCUSSION

With use of single-frequency rotational stimulation, our data show no evidence for vestibular recruitment, ie, no abnormal growth of response, in patients with Meniere's disease. The discrepancy between the results of our study and the results of others[1-7] may relate either to the type of stimulus used or to the patient population sampled. Caloric stimulation, used in several previous studies,[1-3] differs from rotation in that 1) it is a thermal rather than a natural stimulus, 2) it stimulates each ear individually, and 3) it has an equivalent frequency of about 0.003 Hz,[14] which is much lower than the rotational frequencies used in this study. The capability of caloric irrigation to stimulate each ear separately may make it a preferred stimulus for detecting an abnormal growth of response. However, the large variability in the response to caloric irrigation,[15] and the long time period required between irrigations, make the use of graded caloric stimuli impractical clinically.

Other types of rotational stimulation, such as the constant acceleration stimuli (velocity trapezoids) used by Mendel,[6] also may be more suitable than sinusoidal rotation for the detection of vestibular recruitment, because cupular deviation is unidirectional with such stimuli. However, unless excessive rotational velocities are employed, practical constant acceleration stimuli are either near the threshold for inducing a measurable eye movement response or are so short-lived that data analysis is difficult.

Our clinical sample consisted of patients whose most recent episode of Meniere's disease occurred several months prior to testing. As a result, these patients may not have shown vestibular recruitment because their otologic condition was quiescent. This attribute of our sample may account, in part, for the differences between our results and those of previous investigators. However, patients with Meniere's disease in the midst of an acute exacerbation are unlikely to permit vestibular testing; therefore, to be clinically useful in assessing patients with Meniere's disease, vestibular recruitment must be detectable during remissions or at least at times other than during acute exacerbations. Also, if vestibular recruitment is directly analogous to the auditory phenomenon, a prerequisite condition is decreased vestibular sensitivity, ie, partial vestibular loss. This condition is not necessarily characteristic of the Meniere's patient, who indeed may be hypersensitive.

Our data regarding the growth of vestibular response with increasing stimulus intensity suggest that the vestibulo-ocular reflex behaves as a linear system for both normal subjects and Meniere's patients. This finding supports the idea that linear system parameters such as gain and phase are appropriate descriptors of the vestibulo-ocular reflex, even in patients with Meniere's disease. The central vestibular system possibly is able to compensate for peripheral vestibular lesions in such a way that the overall vestibulo-ocular reflex behaves linearly, thus masking underlying nonlinearities such as an abnormal growth of response. Other, not-yet-developed vestibular testing techniques (eg, vestibular evoked potential measurement) that do not rely on the vestibulo-ocular system may be able to uncover peripheral vestibular recruitment. Nevertheless, the use of multiple stimulus amplitudes may be of benefit when one is testing patients suspected of other vestibular disorders, wherein stimulus magnitude-dependent changes in phase or asymmetry may be of clinical use.[16]

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IDENTIFICATION AND CHARACTERIZATION OF MIDDLE EAR VASCULAR LEAKAGE SITES IN EXPERIMENTAL OTITIS MEDIA

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UMEÅ, SWEDEN

The site of leakage in middle ear vessels was determined and characterized in experimental otitis media in rats. Middle ear effusion was induced by intravenous administration or local application in the tympanic bulla of substance P (SP), acetylcholine, and histamine. In another experiment, a 14°C airstream was blown into the external auditory canal. Colloidal carbon was used to trace leakage sites at the light and electron microscopic levels. All mediators tested and the 14°C airstream resulted in an increased number of leaking vessels in the pars flaccida and the middle ear mucosa. The leakage sites were restricted to capillaries and postcapillary venules. Increased numbers of degranulated pars flaccida mast cells were observed for SP only. Interendothelial gaps formed in leaking vessels after administration of mediators and stimulation of the external auditory canal with a 14°C airstream. Also, cytoplasmic vesicle-like structures within the endothelial cells increased in number following SP and histamine treatment, suggesting that an increased permeability in experimental otitis media does not occur exclusively through interendothelial gaps.

KEY WORDS — capillaries, colloidal carbon, mast cells, middle ear mucosa, pars flaccida, postcapillary venules, vessel permeability.

INTRODUCTION

Vascular leakage is recognized as a pathogenetic factor in otitis media with effusion.[1,2] Twenty-four hours after blockage of the eustachian tube in animals, colloidal carbon, used as a marker for vascular leakage, was seen in the wall of middle ear vessels.[2] Abundant mast cells are found in the middle ear mucosa and in particular in the pars flaccida of the tympanic membrane.[3] A possible involvement of these middle ear mast cells was suggested in the effusion production.

Apart from histamine, other vasoactive mediators have been identified in the rat middle ear mucosa, such as the neuropeptides substance P (SP), vasoactive intestinal polypeptide, and calcitonin gene-related peptide.[4,5] The SP and calcitonin gene-related peptide immunoreactive nerve fibers are abundant in the pars flaccida, but less so in the pars tensa.[6] Acetylcholinesterase-positive fibers have been identified in the rat pars flaccida (P. Goldie, S. Hellström, S. Forsgren; unpublished data, 1988), and acetylcholine (Ach) has also been shown to increase middle ear vessel permeability.[7] All these vasoactive mediators could be involved in the early stages of increasing vessel permeability in otitis media with effusion. The aim of the present study was to determine and to compare the distribution of leaking middle ear vessels, to identify the leaking vessels, and to characterize possible changes in the endothelial cells promoting the permeability increase in experimental otitis media induced by vasoactive mediators.

MATERIAL AND METHOD

Male Sprague-Dawley rats weighing 250 to 300 g were used. The animals were anesthetized with sodium pentobarbital (Mebumal 60 mg/mL per kilogram body weight) intraperitoneally. Commercial ink was filtered (Munktell filter paper, Stora, Grycksbo, Sweden), and without resuspension the colloidal carbon particles (1 mL per kilogram body weight; Pelikan India Drawing Ink, Pelikan Ag, Hannover, Federal Republic of Germany) were injected intravenously immediately prior to the administration of test drugs (see below). The diameter of the carbon particles was determined on electron micrographic prints at a final magnification of 19,800. The particles measured 40 nm. The injected carbon is cleared from the circulation within 1

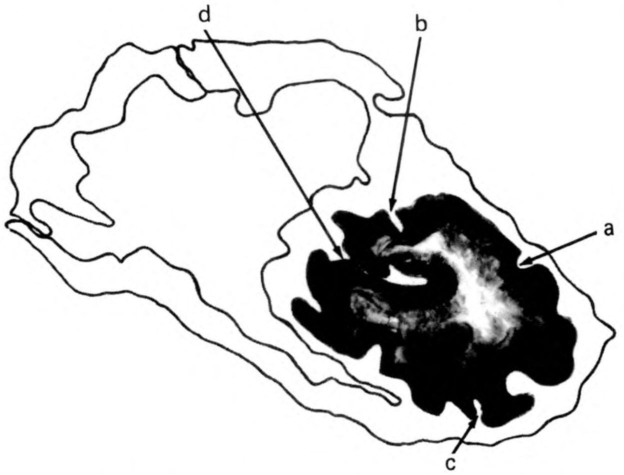

Fig 1. Endothelial cell nucleus exhibiting notch, ie, indentation with converging sides (a), fold with parallel sides (b), closing fold with constriction at mouth (c), and pinch, ie, opposing surfaces pressed together so that nuclear membrane comes in contact along part or all of fold (d).

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TABLE 1. MACROSCOPIC EVALUATION OF LEAKAGE OF CARBON PARTICLES IN VARIOUS PARTS OF TYMPANIC CAVITY AFTER INTRAVENOUS ADMINISTRATION OF DRUGS OR BY LOCAL APPLICATION

	Mucosa Covering						
Treatment	*Promontory*	*Eustachian Tube Orifice*	*Nasal Fossa*	*Floor of Bulla*	*Occipital Promontorial Sulcus*	*Nasal Promontorial Sulcus*	*Stapedial Artery*
Controls	–	–	–	–	–	–	–
Opening tympanic bulla	–	–	–	–	+	–	–
Saline, local, 0.9%	+	+	+	+	+	–	+
Substance P							
Intravenous	–	+	+	–	+	–	+
Local	+	+	+	–	+	–	+
Acetylcholine							
Intravenous	–	–	–	–	–	–	+
Local	–	–	+	+	–	–	–
Histamine							
Intravenous	–	+	+	–	–	–	+
Local	–	+	+	+	–	–	+
Air, 14°C	–	+	+	–	–	–	+

For anatomic details, see Hellström et al.[11]
Plus — leakage, minus — no leakage.

hour, and extravasated black particles indicate sites of leakage.[8]

Group A: Intravenous Administration of Drugs. Substance P, 11.0 μg/mL per kilogram body weight; Ach, 1.0 mg/mL per kilogram body weight; and histamine, 55.2 mg/mL per kilogram body weight, were injected in a tail vein. Four animals were used for each drug. The concentrations were chosen according to previous experiments.[7] Substance P and histamine were dissolved in 0.9% saline, and Ach, in distilled water. All the drugs were obtained from Sigma Chemical Co, St Louis, Mo.

Group B: Local Application of Drugs. After an incision was made in the ventral portion of the neck, the left tympanic bulla was dissected free, and a small hole was drilled in the bone. A fine cannula attached to a syringe was used to fill the tympanic bulla (50 μL) with 0.9% saline or with SP, Ach, or histamine at the concentrations mentioned above. Three animals were used for each drug. In another three animals, the only intervention was to drill a hole in the floor of the tympanic bulla.

Group C: Stimulation of External Auditory Canal. In four animals, a 14°C airstream was blown into the left external auditory canal (EAC) at an airflow rate of 2.5 L/min for 20 minutes, a procedure known to cause middle ear fluid accumulation.[9]

Group D: Controls. In four animals, colloidal carbon was injected intravenously, without injection of any other drugs.

Fixation Procedures. One hour after the administration of colloidal carbon, three animals per drug (or other treatment) in groups A, C, and D were fixed by perfusion with 3% glutaraldehyde in 0.075 N cacodylate buffer (20 mL/min for 10 minutes at a hydrostatic pressure of 120 cm water) through a cannula in the left ventricle of the heart. The remaining animal in each group was fixed by immersion in the same fixative. In group B, all three animals were fixed by perfusion as described above.

TABLE 2. NUMBER OF LEAKING VESSELS EXPRESSED AS PERCENTAGE OF TOTAL NUMBER OF PARS FLACCIDA AND STAPEDIAL MUCOSAL VESSELS, RESPECTIVELY

	Pars Flaccida Vessels		*Mucosal Lining Vessels*	
Treatment	*Intravenous Administration*	*Local Application*	*Intravenous Administration*	*Local Application*
Controls	4.0 (0-10.0)		11.5 (5.8-15.6)	
Opening tympanic bulla		15.5 (12.9-20.4)*		35.9 (24.5-41.4)*
Saline, 0.9%		19.2 (11.5-21.1)*		25.0 (17.9-29.0)*
Substance P	30.0 (23-40.0)*	19.4 (15.4-23.3)*	46.5 (41.2-57.1)*	35.3 (21.3-40.9)*
Acetylcholine	17.5 (7-21.5)*	23.9 (20.4-27.4)*†	26.2 (20.4-33.3)*	52.9 (26.8-70.7)*§
Histamine	25.0 (17-31.0)*	25.0 (19.0-27.4)*†	42.1 (30.8-50.0)*	46.2 (40.3-50.0)*†§
Air, 14°C	21.5 (15-24.0)*		47.3 (33.3-58.8)*	

Figures represent median and first and third quartiles.
*Significant increase compared with controls: $2p<.05$.
†Significant increase compared with opening of tympanic bulla alone: $2p<.05$.
§Significant increase compared with 0.9% saline: $2p<.05$.

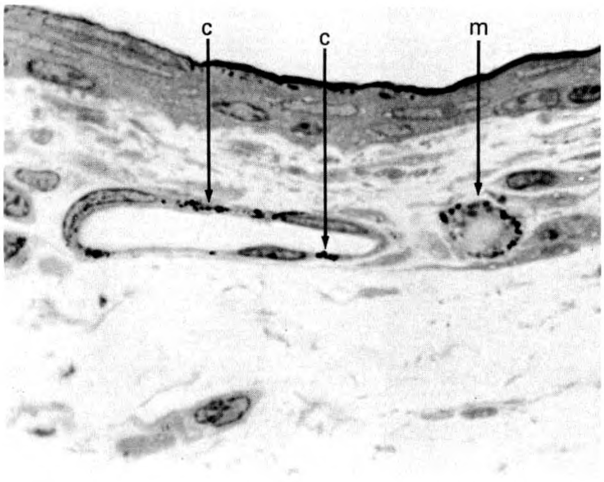

Fig 2. Light micrograph of perfusion-fixed specimen showing carbon particles (c) in wall of vessel in vicinity of mast cell (m) in pars flaccida from animal subjected to 14°C airstream in external auditory canal (original x400).

After fixation, the pars flaccida and the stapedial artery with its mucosal lining were carefully excised, immersion-fixed in 1% osmium tetroxide in 0.1 N cacodylate buffer for 2 hours, dehydrated in graded series of acetone, and embedded in an epoxy resin. Semithin (1 μm) sections were cut and stained with toluidine blue for light microscopy. Specimens from groups A, C, and D were also cut into ultrathin sections (80 nm), stained with uranyl acetate and lead citrate, and inspected in an electron microscope (JEOL XS 100 EM). The perfusion-fixed specimens were used for quantitative light microscopic evaluations and statistical analysis.

Light Microscopic Evaluation. Four sections from each tissue sample were collected from two different levels 100 μm apart. The thickness of the sections from the pars flaccida and the stapedial artery, including the mucosal lining, was measured. For each section the thickness was estimated as an average of values obtained from three different locations. Vessels exhibiting carbon particles in their walls were classified as leaking vessels. These were counted for each section and expressed as a percentage of the total number of pars flaccida or mucosal lining vessels. The diameter of the leaking vessels was also measured by computerized (MOP-Videoplan) morphometric techniques. The number of degranulated mast cells was calculated for each section of the pars flaccida and expressed as a percentage of the total number of mast cells found in that pars flaccida section. Degranulated mast cells were identified as mast cells with broken contours and granules in their vicinity.

The median and first and third quartiles were determined for each investigated parameter and each treatment. Statistical analysis was performed by the nonparametric Mann-Whitney test. Differences were considered significant when $2p < .05$.

Electron Microscopy. Sections from immersion- and perfusion-fixed specimens were examined and photographed at magnifications of 3,000, 6,600, and 8,300, and the various parameters were estimated on prints three times the original magnification. The following parameters were investigated: 1) the diameter of the leaking vessels, 2) the location of extravasated carbon particles in relation to the basement membrane and vesicle-like endothelial cell structures, 3) cells adhering to the endothelium, and 4) the occurrence of interendothelial gaps. Measurement of the diameter of the vessels included the vessel wall to the basement membrane. The shape of the endothelial cell nucleus was also examined according to the criteria set up by Majno et al[10] for endothelial cell contraction (Fig 1).

RESULTS

Macroscopic Evaluation. No fluid and no carbon particles were seen in the middle ear cavity of control animals. After simply opening the floor of the tympanic bulla or local application of 0.9% saline, occasional carbon particles were seen in the middle ear mucosa (Table 1[11]). After intravenous injection of SP and Ach, fluid was seen in the medial attic compartment. No fluid was seen in the middle ear cavities of animals treated with intravenous histamine. All drugs, whether injected intravenously or applied locally, caused carbon particles to appear in the middle ear mucosa (Table 1). In middle ears that had been subjected to a 14°C airstream, fluid filled the attic space and reached the mesotympanum. Carbon particles were seen in the middle ear mucosa.

Light Microscopic Evaluation. The diameter of leaking vessels ranged between 2.2 and 41.6 μm. All the drugs tested caused leakage in the whole range of vessel sizes.

Injection of only colloidal carbon caused extravasation of carbon particles in a few of the vessels (Table 2). The number of carbon-labeled vessels was significantly increased after intravenous administration of SP, Ach, histamine, or a 14°C airstream in the EAC (Table 2 and Fig 2). The leaking vessels were more numerous in the stapedial mucosal lining than in the pars flaccida. In the stapedial mucosal lining, local application of SP, Ach, and histamine significantly increased the number of carbon-labeled vessels compared with that in control animals. However, only histamine increased the number of carbon-labeled vessels vis-à-vis local application of 0.9% saline and simply opening the tympanic bulla. In the pars flaccida, local application of SP, Ach, and histamine increased the number of leaking vessels compared with that in control animals. However, there was no significant difference between the number of leaking vessels in animals that received drugs locally and that of animals that received only 0.9% saline locally.

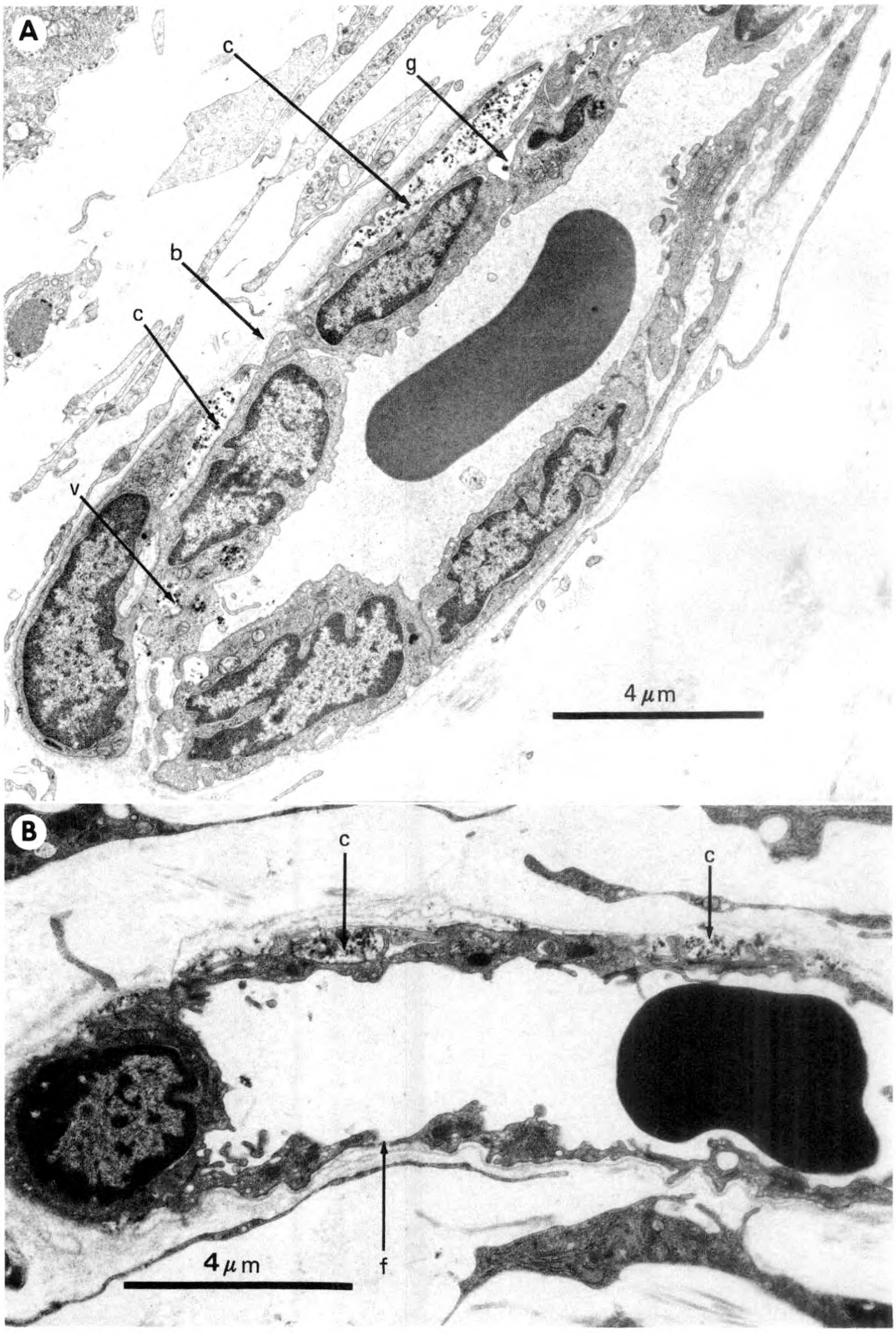

Fig 3. Immersion-fixed specimen from animal that received intravenous substance P. A) Pars flaccida vessel containing carbon particles (c) in vesicle-like structures (v), within interendothelial gaps (g), and arrested by basement membrane (b). B) Vessel in stapedial mucosa exhibiting carbon particles (c) in its wall. Possible fenestration in endothelium is indicated (f).

Pars flaccida thickness increased in all groups, including those in which only the floor of the tympanic bulla had been opened, compared with control animals. When drugs were applied locally there was no further increase in pars flaccida thickness compared to that after 0.9% saline. The stapedial artery mucosa thickness was increased only after intravenous administration of SP.

Only intravenous and local application of SP caused a significant increase in the number of degranulated mast cells in the pars flaccida versus control animals with drilling only or local application of 0.9% saline only. For intravenous SP, the median increase was 13% (range, 6% to 17.3%); for local application of SP, the median increase was 7.7% (range, 1.1% to 8.2%).

Electron Microscopy. The findings were the same for the pars flaccida and the stapedial mucosal lining. Leukocytes were not seen to adhere to the endothelium in any of the sections.

In the control animals, no extravasated carbon particles were identified. The nuclear membranes were irregular, exhibiting notches, folds, and closing folds. In SP-, Ach-, and histamine-treated animals, some widened interendothelial junctions con-

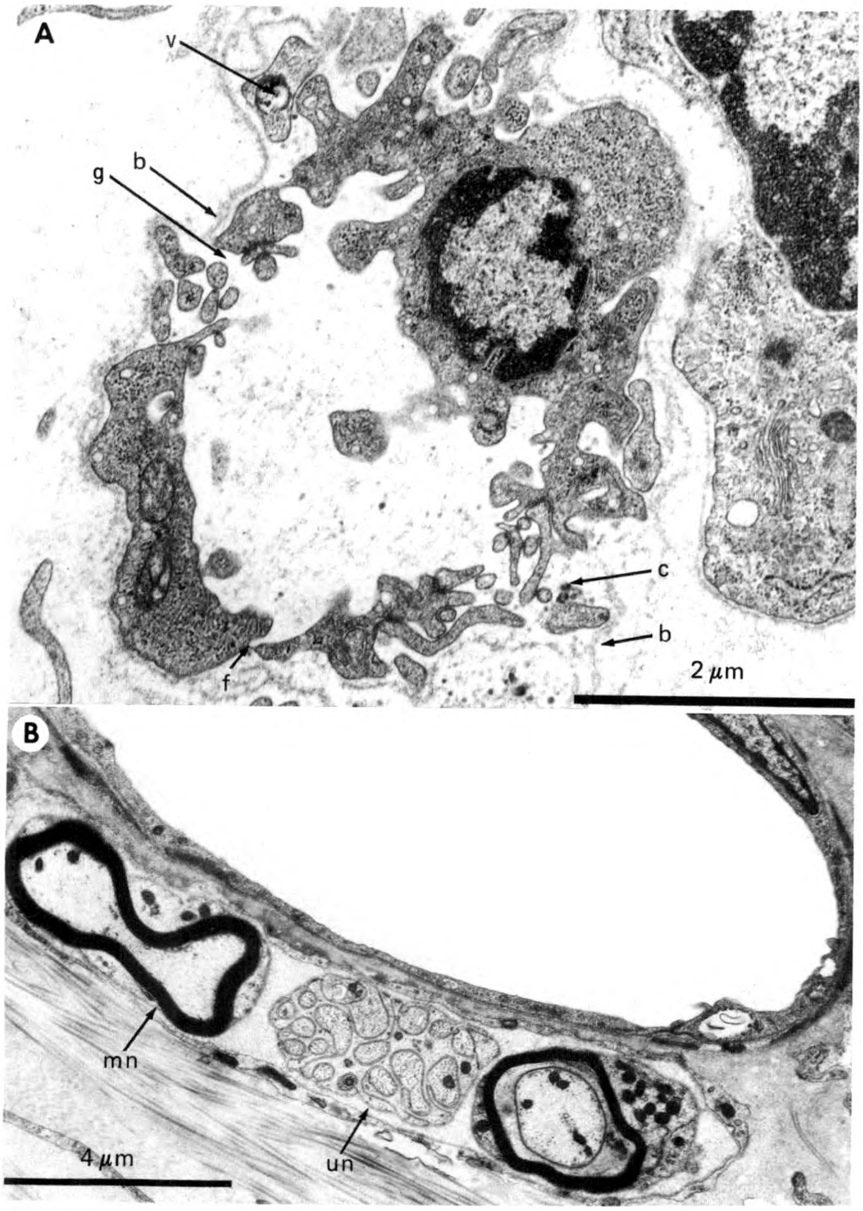

Fig 4. Specimens from stapedial mucosa of animal that received intravenous acetylcholine. A) Immersion-fixed specimen of small vessel exhibiting interendothelial gaps (g) and showing carbon particles (c) arrested by basement membrane (b) and within vesicle-like structures (v). Possible fenestration in endothelium is indicated (f). B) Perfusion-fixed specimen of unmyelinated (un) and myelinated (mn) nerves in vicinity of vessel.

tained carbon particles. Carbon particles were also found adjacent to the basement membrane and occasionally within vesicle-like structures of the endothelial cells. The number of these structures was significantly greater for SP and histamine groups than in control animals. The nuclei showed the same irregular shape as in control animals, but also exhibited pinches (Figs 3 and 4). In the animals stimulated with a 14°C airstream in the EAC, carbon particles were found adjacent to the basement membrane only. Some interendothelial gaps were observed. Only occasional pinches were detected in the irregularly shaped endothelial cell nuclei (Fig 5).

The diameter of the smallest leaking vessel observed in the electron micrographs, including the vessel wall to the basement membrane, was 4.3 µm. The diameter of leaking vessels in immersion- and perfusion-fixed specimens did not differ.

DISCUSSION

Substance P, Ach, histamine, and stimulation of the EAC with a 14°C airstream all caused an increased permeability in the pars flaccida as well as in the middle ear mucosal vessels. There was no correlation between the amount of middle ear fluid and the extent of extravasated carbon particles; this was also the case in experimentally elicited serous otitis media.[2]

Mediator-Induced Increase in Capillary Permeability. The smallest vessels showing carbon particle deposits in their walls had a lumen diameter of 2.2 µm and approximately 4 to 5 µm diameter if the vessel wall was included. The wall in these vessels consisted solely of endothelial cells, corresponding to capillaries.[12] The largest vessel leaking carbon particles measured 41.6 µm in lumen diameter. The vessel wall was composed of endothelial cells and

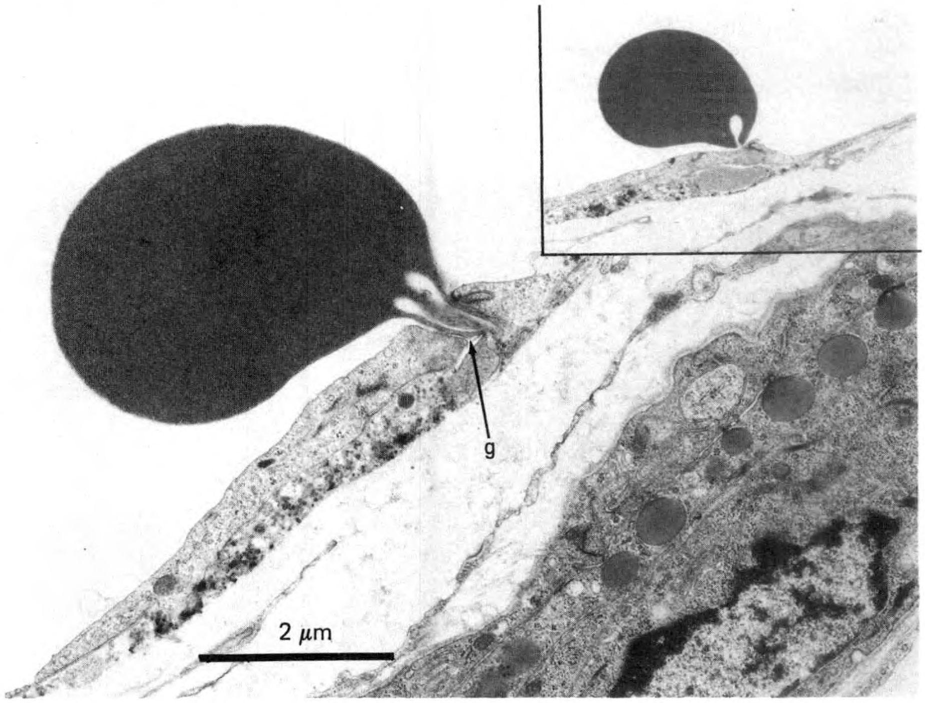

Fig 5. Perfusion-fixed specimen taken from stapedial mucosa of animal stimulated with 14°C air-stream in external auditory canal, showing red blood cell traversing vessel wall through interendothelial gap (g). Inset) Detail of adjacent section.

pericytes, corresponding to postcapillary venules.[12] Thus, leakage in middle ear vessels was observed in capillaries as well as in postcapillary venules, independent of the experimental situation. In previous investigations, leakage has been restricted to postcapillary venules larger than 7 μm in diameter.[13,14] An increased permeability in capillaries under inflammatory conditions has been suggested, though,[15] and the present investigation adds further evidence to support this hypothesis. However, the middle ear vessels appear to react differently from other vascular beds, not only with respect to capillary leakage, but also when considering different receptor populations. The increase in middle ear vessel permeability following cold air stimulation was found to be H2 receptor–dependent,[7] in contrast to skin vasculature, in which increase in vessel permeability is mediated by H1 receptors.[16] The small diameter of the leaking vessels in the present study ought not to be attributed to shrinkage due to fixation procedures, since the diameter of red blood cells in vessels of the pars flaccida and the middle ear mucosal lining measured 6.3 μm, which is within the normal range for rat erythrocytes.[17]

The middle ear vessels showed a striking reactiveness. The trauma of opening the tympanic bulla only, or after instillation of 0.9% saline, was sufficient to increase the permeability of the pars flaccida and middle ear mucosal vessels.

The fact that local application of SP did not increase the number of leaking middle ear vessels to the same extent as intravenous SP could be due to a rapid breakdown of SP by tissue enzymes. One candidate for SP degradation is cathepsin D,[18] which has been identified in middle ear effusions[19] and should occur in the middle ear mucosa.

Transmural Movement of Carbon Particles. Similar changes in the endothelial cells were induced in all groups. Carbon particles crossed the endothelial wall through interendothelial gaps. Interendothelial gap formation has previously been shown for histamine and serotonin in vessels of the cremaster muscle.[8] To form gaps, the endothelial cells are thought to contract, thus increasing the nuclear folds, especially pinches.[10] We were able to show similar structural changes in the middle ear endothelial cell nuclei, which were particularly noticeable after injection of SP and histamine. Carbon-containing structures resembling vesicles were also seen within the endothelial cells. Transendothelial movement of macromolecules, eg, ferritin, by vesicles has been proposed to be a major route under normal conditions.[20] This view has been opposed by other authors.[21,22] When capillaries are serially sectioned, what appear to be free vesicles are seen to be actually multilocular invaginations from luminal and abluminal surfaces of endothelial cells. These invaginations are proposed to allow the cell to regulate its cytosolic free calcium concentration. In the present study, the increase in vesicle-like structures in endothelial cells after SP and histamine administration might represent an increase in endothelial cell invaginations, reflecting an increase in the calcium flux across the endothelial plasmalemma.

The mere injection of carbon particles caused leakage in a small number of pars flaccida and stapedial artery mucosal vessels, a phenomenon also observed in experimentally induced serous otitis media.[2] Notably, fenestrated capillaries were observed in some of the middle ear vessels (Figs 3B and

4A).

Neurogenic Inflammation in Otitis Media With Effusion. In the present study we demonstrated an increased number of degranulated mast cells in SP-treated animals. In previous studies of an otitis media model, we proposed neurogenic inflammation as a mechanism for increasing middle ear vessel permeability.[23] Mast cells and SP-containing nerves are thought to interact, resulting in vasodilation and edema.[24] The facts that 1) SP increases middle ear vessel permeability,[7] 2) SP-containing nerve fibers are located close to mast cells in the pars flaccida,[6] and 3) elevated histamine levels are detected in middle ear effusions[25] render it likely that neurogenic inflammation is one of the mechanisms involved in vessel permeability changes in otitis media with effusion.

Concluding Remarks. All the mediators studied in the present investigation induced similar endothelial cell changes, promoting a permeability increase in various regions of the middle ear. Vascular permeability changes were not restricted to postcapillary venules, but were also observed in capillaries. The major route for increasing vessel permeability is the opening of interendothelial junctions. Whether vesicles in the endothelium really exist and represent a route for transendothelial transport of macromolecules can still be questioned. Possible neurogenic mechanisms involved in the pathogenesis of otitis media with effusion, which have been proposed in the present and in previous investigations,[23] will be the subject of future studies.

ACKNOWLEDGMENT — The authors thank Associate Professor Anders Bergh for reviewing the manuscript.

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Ann Otol Rhinol Laryngol 99:1990

IMMUNO-ELECTRON MICROSCOPIC STUDY OF KERATIN DISTRIBUTION IN THE COCHLEA USING MONOCLONAL ANTIBODY

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Keratin distribution in the cochlea has been studied immuno-electron microscopically by both pre-embedding and postembedding methods. Keratin immunoreactivity in the guinea pig cochlea was clearly demonstrated in Hensen's cells, the reticular lamina surrounding both outer and inner hair cells, outer and inner pillar cells, Claudius' cells, inner and external sulcus cells, interdental cells of the spiral limbus, Reissner's membrane, border cells, inner phalangeal cells, Deiters' cells, and spiral prominence cells. Keratin expression at the ultrastructural level showed a nonfilamentous keratin system in the cytoplasm of cochlear supporting cells.

KEY WORDS — antibody, cochlea, electron microscopy, immunohistochemistry, keratin, ultrastructure.

Keratin distribution in the cochlea has been studied immunohistochemically by light microscopy.[1-6] However, it has not been studied immuno-electron microscopically. As a marker for epithelial cells, the immunohistochemical localization of keratin has increasingly been used for both theoretic and clinical research.[7-13] Studies of keratin localization in the cochlea by light microscopy are not conclusive. Aniko et al[14] studied several intermediate filament proteins for localization in the newborn mouse inner ear by an immunofluorescence technique using frozen sections and did not demonstrate keratin staining in cochlear cells. In addition, the function of keratin protein in cochlear cells has not yet been

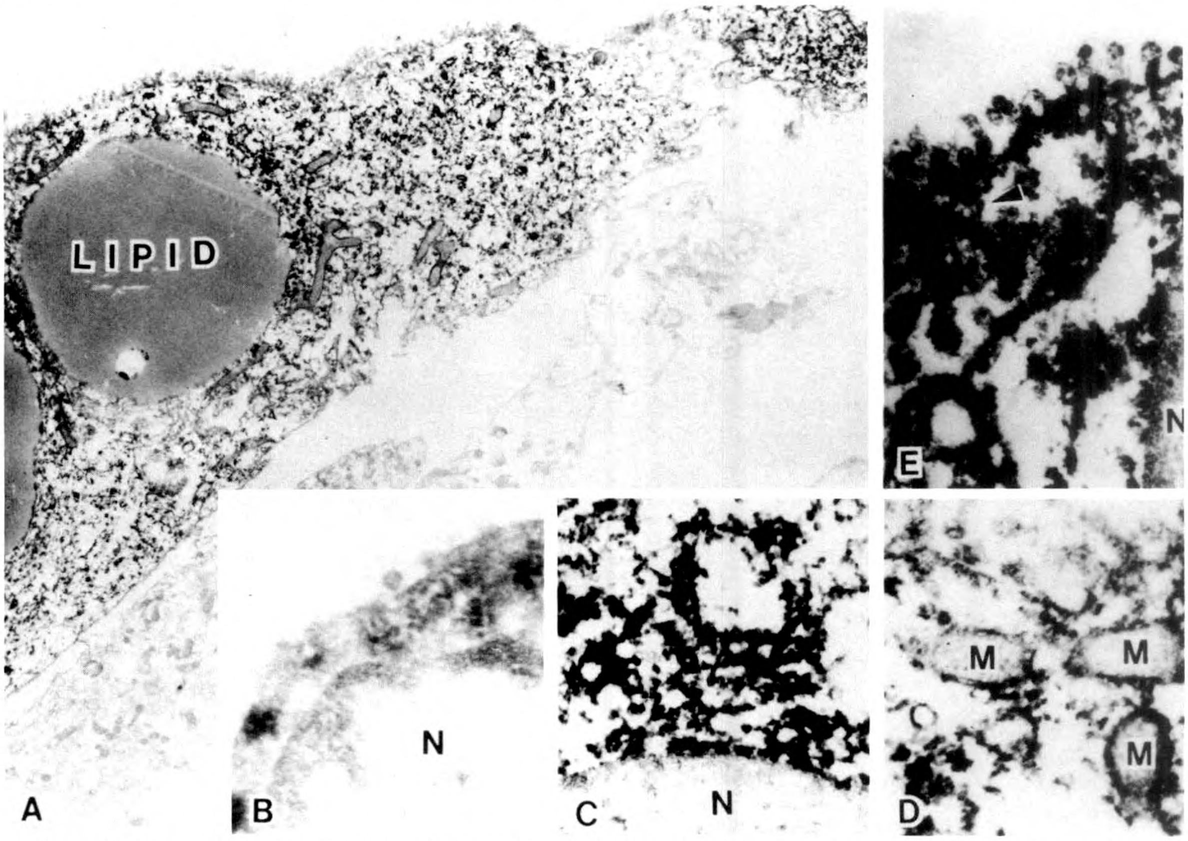

Fig 1. Characteristic ultrastructural localization of keratin in Hensen's cell by saponin-treated pre-embedding method without counterstaining. N — nucleus. A) Diffuse abundant keratin-positive structures resembling network of nonfilamentous keratin system (NFKS) (original x2,500). B) Postembedding method showing keratin distribution in Hensen's cell (original x20,000). C) Fine granular and filamentous network (original x10,000). D) Mitochondria (M) surrounded by keratin-positive structure (original x15,000). E) Tubular structure (arrowhead) (original x10,000).

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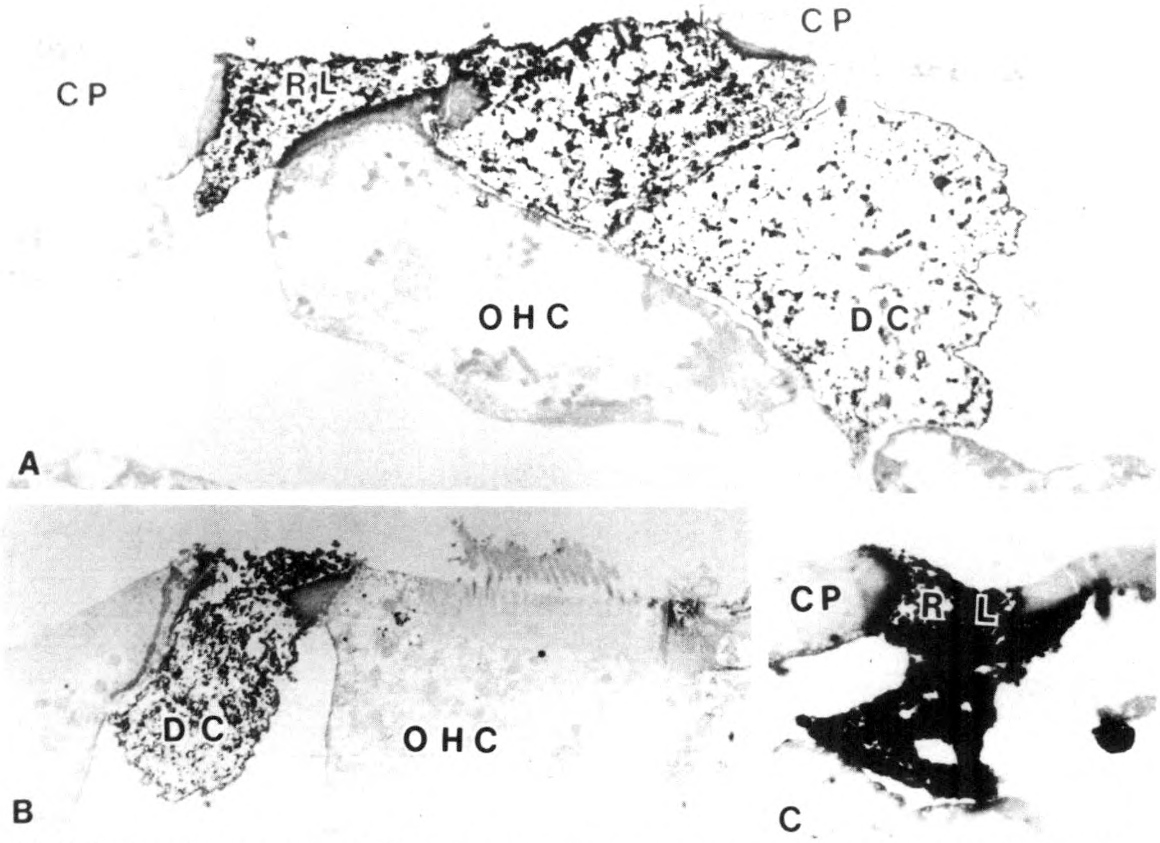

Fig 2. Immuno-electron microscopic localization of keratin in apical region of Deiters' cell (DC) (original x3,000). A,B) Pre-embedding method without counterstaining. OHC — outer hair cell, CP — cuticular plate. A) Triton X-100-treated tangential section through apical region of organ of Corti showing strong keratin-positive reticular lamina (RL) of DC. Upper portion of DC was also labeled by AE1. Tight junction showed clearly positive staining. B) Saponin-treated radial section showing sharp border between RL and CP. C) Similar radial section stained by postembedding method.

determined. In contrast to the extensive studies of actin filaments in cochlea,[15-17] the information on keratin is far from satisfactory. The aim of our study was to demonstrate ultrastructural localization of keratin in cochlear cells and to develop a technical protocol for future studies.

MATERIALS AND METHODS

TISSUE PREPARATION

Normal guinea pigs (300 to 900 g) with good Preyer's reflex were anesthetized by an intraperitoneal injection of Nembutal sodium solution (50 mg/kg). Temporal bones were removed rapidly after quick decapitation or intracardial perfusion with freshly prepared PLP (0.01 mol/L periodic acid, 0.075 mol/L lysine, and 2% paraformaldehyde).[18] After removal of the temporal bone, the apex of the cochlea was opened, the stapes was removed, and the perilymphatic spaces were perfused with PLP. Two or three small holes were opened in the coch-

IMMUNO-ELECTRON MICROSCOPIC LOCALIZATION OF KERATIN IN COCHLEAR CELLS

Cell	*Localization*	*Ultrastructural Features*	*Figure*
Hensen's	Diffuse abundant in CPM, surrounding M, MV, CM, and N	Fine granular, filamentous, tubular keratin-positive network	1
Deiters'	Upper and lower CPM adjacent to BM mainly in RL, surrounding M	Fine granular and filamentous network, keratin-positive TF seen in lower CPM	2, 3
Border and inner phalangeal	Diffuse in CPM mainly in RL	Fine granular and filamentous network, hairlike structure in apical region of border cell	4
Pillar	Along borderline of upper CPM mainly in IPP, surrounding M	Fine granular appearance, TF stained weakly to moderately	5, 6
Interdental	Diffuse abundant in CPM surrounding M	Similar to Hensen's cell, tubular structure seen in apical CPM	7
Claudius' and inner sulcus	Mainly in apical CPM	Fine granular appearance	8
Reissner's membrane	Diffuse abundant in CPM of EL, weakly positive in ML	Similar to Hensen's cell	8
Spiral prominence and external sulcus	Diffuse abundant in CPM	Similar to Hensen's cell	9

CPM — cytoplasm, M — mitochondria, MV — microvilli, CM — cell membrane, N — nucleus, BM — basilar membrane, RL — reticular lamina, IPP — inner pillar phalanx, EL — epithelial layer, ML — mesothelial layer, TF — tonofilaments.

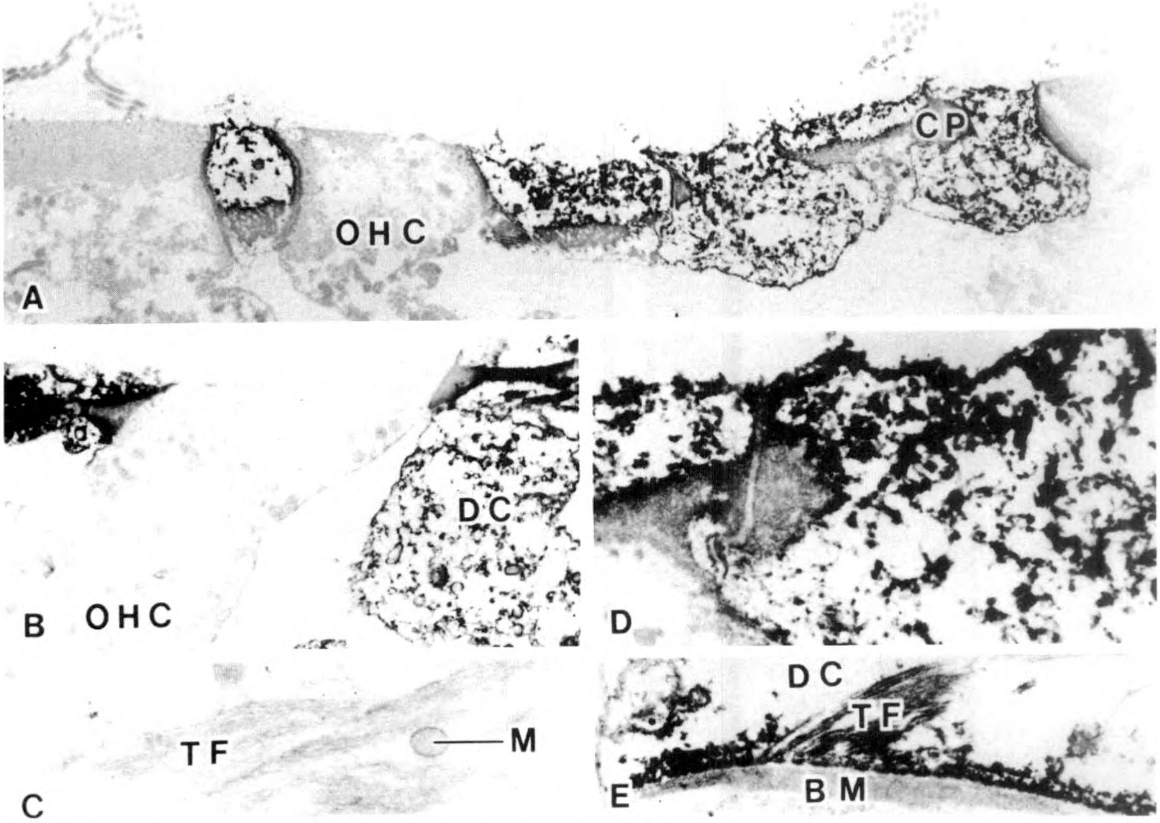

Fig 3. Immuno-electron microscopic localization of Deiters' cell (DC) showing junctional connection between reticular lamina and cuticular plate (CP) by pre-embedding method without counterstaining. OHC — outer hair cells. A) Triton X-100-treated tangential section through apical region of organ of Corti (original x3,000). Note sharp border between reticular lamina (positive) and CP (negative). B) Saponin-treated (original x5,000). Comparison between mitochondria in DC (surrounded by keratin-positive structure) and mitochondria in OHC (negative). C) Saponin-treated (original x10,000). Tonofibrils (TF) in lower portion of DC labeled weakly positive to AE1. Note mitochondria (M) surrounded by keratin-positive structure. D) Triton X-100-treated (original x10,000). Fine granular and filamentous NFKS in reticular lamina of DC. E) Saponin-treated (original x8,000). Bottom of DC showing keratin-positive TF and positive line along border with basilar membrane (BM), which was keratin-negative.

lear coils for the postembedding method. For the pre-embedding method, most of the bony wall of the cochlea was removed. The spiral ligament, the stria vascularis, and Reissner's membrane were partly removed to expose the organ of Corti. All cochleas were fixed by immersion in PLP at 4°C for 1.5 hours, followed by a 90-minute rinse in three changes of either 7% sucrose phosphate buffer solution (PBS) for the postembedding method or 7% sucrose PBS plus saponin or Triton X-100 for the pre-embedding method, and left in the same solution overnight. One specimen was prepared for the pre-embedding method according to the surface preparation technique as previously reported.[19]

ANTIBODIES AND REAGENTS

The monoclonal keratin antibody AE1, provided by T. T. Sun, New York University, was prepared by the hybridoma technique. It reacts with the 40-, 50-, and 56.5-kd classes of keratin proteins identified by the immunoblotting technique.[7-9] Immunohistochemical staining results reported thus far have shown that antibody AE1 recognizes almost all epithelia and does not cross-react with nonepithelial tissues.[7-9,11] The avidin biotin peroxidase complex (ABC) kits were obtained from Vector Laboratories, Inc, Burlingame, Calif. Chemical reagents were obtained from Wako Pure Chemical Industries, Ltd, Osaka, Japan.

IMMUNOHISTOCHEMICAL STAINING PROTOCOL

Pre-embedding Method. After fixation, we used 1 mg/mL saponin (Sigma Chemical Co) in 7% sucrose PBS for three changes and overnight; sometimes 0.3% Triton X-100 was used instead of saponin. Next morning, the tissue was placed in fresh PBS for 30 minutes, followed by use of the three-step ABC method as previously described.[20] Briefly, the following incubations were performed on either the whole cochlea or the dissected cochlear segments: 1) normal horse serum at 4°C for 1 hour, 2) without rinsing, incubation with monoclonal keratin antibody AE1 at a dilution of 1:1 overnight at 4°C, 3) biotinylated horse anti mouse antiserum at a dilution of 1:200 for 30 minutes at 37°C, 4) ABC at a dilution of 1:100 for 30 minutes at 37°C, 5) between incubations (steps 2, 3, and 4), rinsing in three changes of PBS for 90 minutes, 6) diamino-

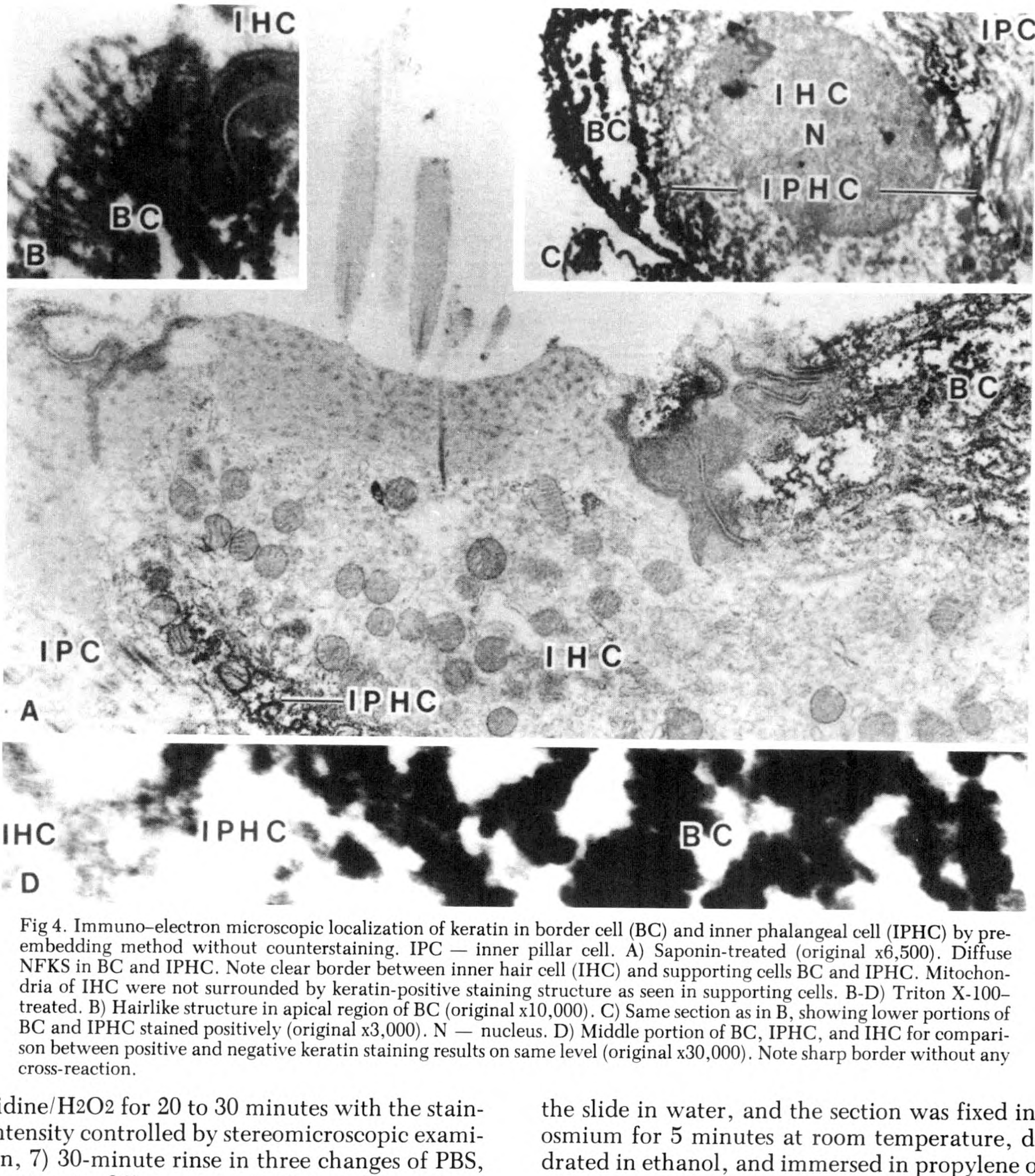

Fig 4. Immuno–electron microscopic localization of keratin in border cell (BC) and inner phalangeal cell (IPHC) by pre-embedding method without counterstaining. IPC — inner pillar cell. A) Saponin-treated (original x6,500). Diffuse NFKS in BC and IPHC. Note clear border between inner hair cell (IHC) and supporting cells BC and IPHC. Mitochondria of IHC were not surrounded by keratin-positive staining structure as seen in supporting cells. B-D) Triton X-100–treated. B) Hairlike structure in apical region of BC (original x10,000). C) Same section as in B, showing lower portions of BC and IPHC stained positively (original x3,000). N — nucleus. D) Middle portion of BC, IPHC, and IHC for comparison between positive and negative keratin staining results on same level (original x30,000). Note sharp border without any cross-reaction.

benzidine/H_2O_2 for 20 to 30 minutes with the staining intensity controlled by stereomicroscopic examination, 7) 30-minute rinse in three changes of PBS, 8) fixation in 2% osmium in 0.1 mol/L sodium cacodylate buffer (pH 7.2) for 1 hour at 4°C, 9) 30-minute rinse in three changes of PBS, and 10) routine dehydration and Epon embedding protocol.

Postembedding Method. A semithin section (2 to 4 μm) obtained from a PLP-fixed cochlea was mounted on a glass slide. The Epon was etched with ethanolic sodium.[2] Immunohistochemical staining of the mounted section was carried out by routine techniques. The slide was mounted with a drop of glycerol, coverslipped, and examined by light microscopy and photographed. Re-embedding of an immunohistochemically stained (ABC method) semithin section was carried out as previously described.[21] The coverglass was removed by soaking the slide in water, and the section was fixed in 2% osmium for 5 minutes at room temperature, dehydrated in ethanol, and immersed in propylene oxide and then an Epon–propylene oxide mixture 1:1 for 1 hour. The section was then covered with 100% Epon for 2 hours; every 30 minutes more Epon was added to prevent the slide from drying out. A Beem embedding capsule filled with 100% Epon was inverted over the section. The Epon was allowed to polymerize at 60°C for 48 hours. The capsule was removed from the slide by being warmed quickly on an alcohol lamp. The ultrathin sections were cut with a diamond knife.

As a control, normal mouse serum and PBS were used for incubation instead of monoclonal keratin antibody AE1. A piece of skin taken from the auricle of a guinea pig was used as a positive control.

Semithin or ultrathin sections were cut with an

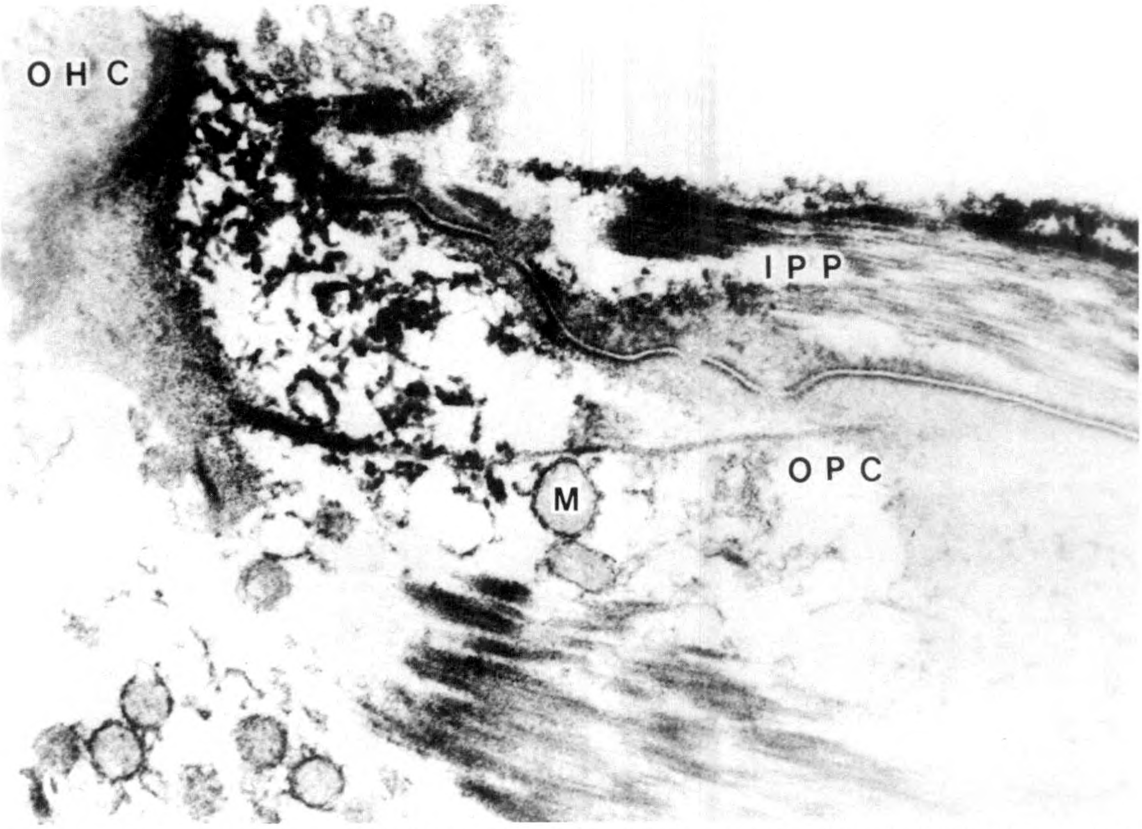

Fig 5. Immuno-electron microscopic localization of keratin in apical region of outer pillar cells (OPC) and inner pillar cells by saponin-treated pre-embedding method without counterstaining, showing strong positive staining of keratin along surface of inner pillar phalanx (IPP) and moderately positive staining for tonofibrils of OPC and inner pillar cells (original x12,000). Granular, filamentous NFKS could be seen in upper cytoplasm of OPC adjacent to outer hair cell (OHC). Mitochondria (M) are surrounded by keratin-positive material.

LKB 4800A ultramicrotome (Sweden). Electron microscopy was carried out with a JEM-1200EX transmission electron microscope (JEOL, Ltd, Tokyo, Japan) with an accelerating voltage of 80 kV.

RESULTS

Both the pre-embedding and the postembedding ultrathin sections showed distinctly positive results with keratin immunoreactivity in some cochlear cells. Tissues prepared by the pre-embedding method were better preserved than those prepared by the postembedding method with respect to morphology and keratin immunoreactivity (Figs 1B,E and 2).

Keratin-positive cells in the cochlea that were identified immuno-electron microscopically are summarized in the Table.

Abundant keratin proteins in Hensen's cells resulted in a network showing three types of keratin-positive structures: granular, filamentous, and tubular structures in between the cell membrane cytoplasm and the nucleus (Fig 1A,C,E). It has been termed the nonfilamentous keratin system (NFKS), as there are no intermediate filaments shown in Hensen's cells by electron microscopy, as previously reported.[22-24] The mitochondria were surrounded by the NFKS (Fig 1D). Keratin-labeled reticular lamina (RL) and the upper part of Deiters' cells showed a sharp border between the cuticular plate (CP) and the RL (Figs 2 and 3). The granular and filamentous types of NFKS were found in the RL and Deiters' cells (Figs 2A and 3D). The mitochondria were also surrounded by the NFKS (Fig 3B,C). The tonofibrils in Deiters' cells were weakly positive by AE1 (Fig 3C,E). The border cells and inner phalangeal cells were stained positively by AE1, showing granular and filamentous types of NFKS (Fig 4A,C,D). A hairlike structure labeled by AE1 was found at the apical region of the border cells (Fig 4B). Keratin distribution in the inner and outer pillar cells was localized predominantly along the borderline of the pillar cells. The tonofibrils in the cytoplasm of the pillar cells were also stained positively by AE1 (Figs 5 and 6). The ultrastructural appearance of the NFKS in interdental cells, the epithelial layer of Reissner's membrane, the spiral prominence cells, and the external sulcus cells was similar to that found in Hensen's cells (Figs 7-9).

All hair cells, mesenchymal cells, blood vessels, basilar membrane, and neural elements were negative to keratin immunohistochemical staining.

None of the negative control sections showed staining with antibodies to keratin, but skin was stained positively by the monoclonal antibody AE1.

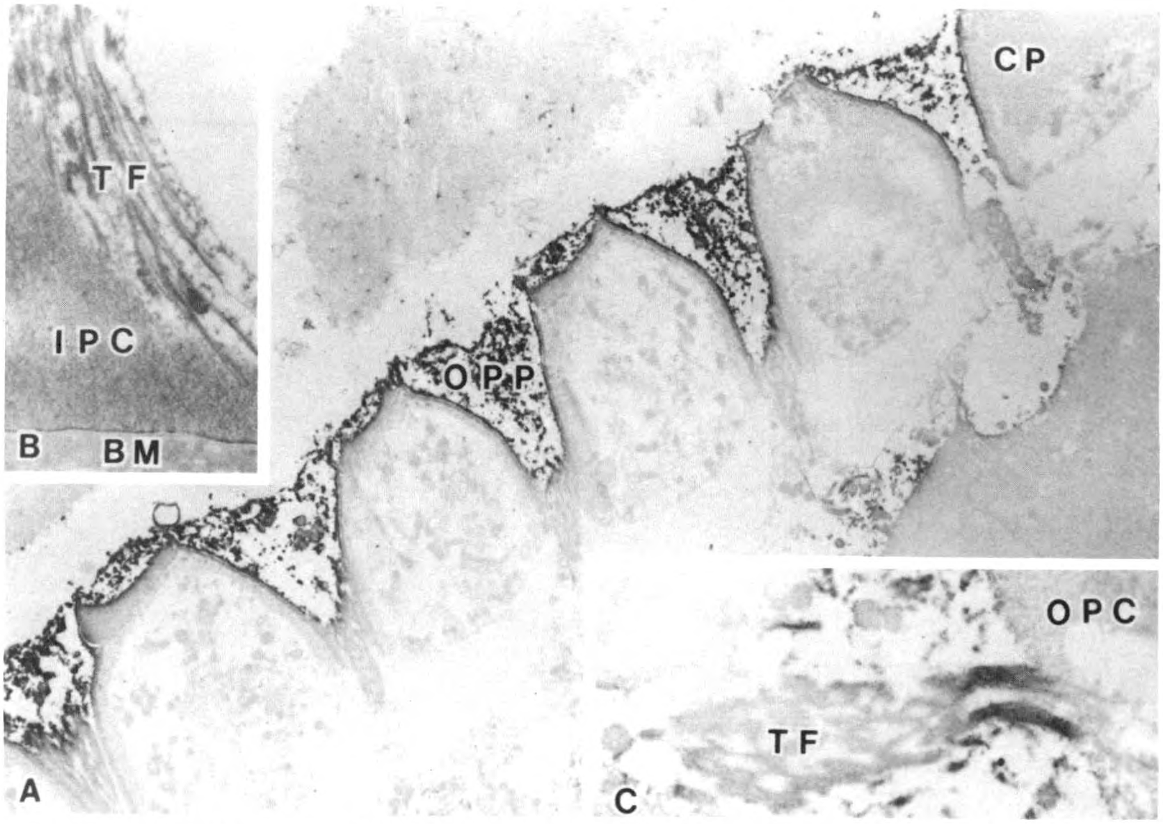

Fig 6. Immuno-electron microscopic localization of keratin in outer pillar cell by Triton X-100–treated pre-embedding method without counterstaining. A) Horizontal section of reticular lamina through first row of outer hair cells showing outer pillar phalages (OPP) stained strongly positive by AE1 (original x2,500). Note weakly labeled tonofibrils that are seen more distinctly in C. CP — cuticular plate. B) Tonofibrils (TF) in lower portion of inner pillar cell (IPC) showing moderate positive staining of keratin and positive line adjacent to basilar membrane (BM) (original x6,500). C) TF of OPP showing weakly positive staining to AE1 (original x10,000). OPC — outer pillar cell.

DISCUSSION

In contrast to the ultrastructural appearance of Hensen's cell, showing only ground substance with scattered mitochondria and numerous tall microvilli,[22-24] the Hensen's cell has dramatically been shown by keratin immunohistochemical staining, particularly when observed immuno-electron microscopically, to have an abundance of keratin-positive structures resembling an NFKS. It suggests to us that Hensen's cell is a highly differentiated cell.[25] A similar NFKS structure was found in the interdental cell of the limbus, showing a tubular structure.

The technique described here may provide an approach to studying the possible secretory function of the interdental cell. Recent studies on cytoskeleton have provided ample evidence that elements of the cytoskeleton play a major role in the process of hormone secretion.[26] The rootlet-like processes of interdental cells extending into surrounding connective tissue stained by keratin antibody may permit a cytoplasmic transportation system between perilymph and endolymph.[27] The new term NFKS may be defined as follows: a keratin protein existing in cytoplasm of certain cells such as Hensen's cell that is not assembled into visible intermediate filaments. Thus far, there has been considerable evidence demonstrating that under physiologic conditions, intermediate filament proteins are primarily assembled, with very little protein found in a soluble pool, and that keratin proteins are entirely assembled into filaments in the cytoplasm.[28] Therefore, there may be a special type of keratin protein in certain cells.

Pillai et al[29] studied growth and differentiation of keratinocytes in different media and found that keratinocytes may lose the morphologic features of epidermal differentiation but still maintain keratin proteins in their cytoplasm. Theoretically, it is possible to have an NFKS in some special cells. Using the peroxidase-antiperoxidase method with the pre-embedding immuno-electron microscopic technique, Langley et al[30] demonstrated that in the Purkinje cell bodies of rodent cerebellum, the majority of neurofilament proteins are not assembled in the form of neurofilaments. Their results are similar to the present data. They found intensely stained diffuse patches in Purkinje cell cytoplasm, but neurofilaments are rarely seen in those perikarya by classic morphologic approaches.

It may be possible to find the NFKS in other supporting cells of the inner ear. A hypothesis concern-

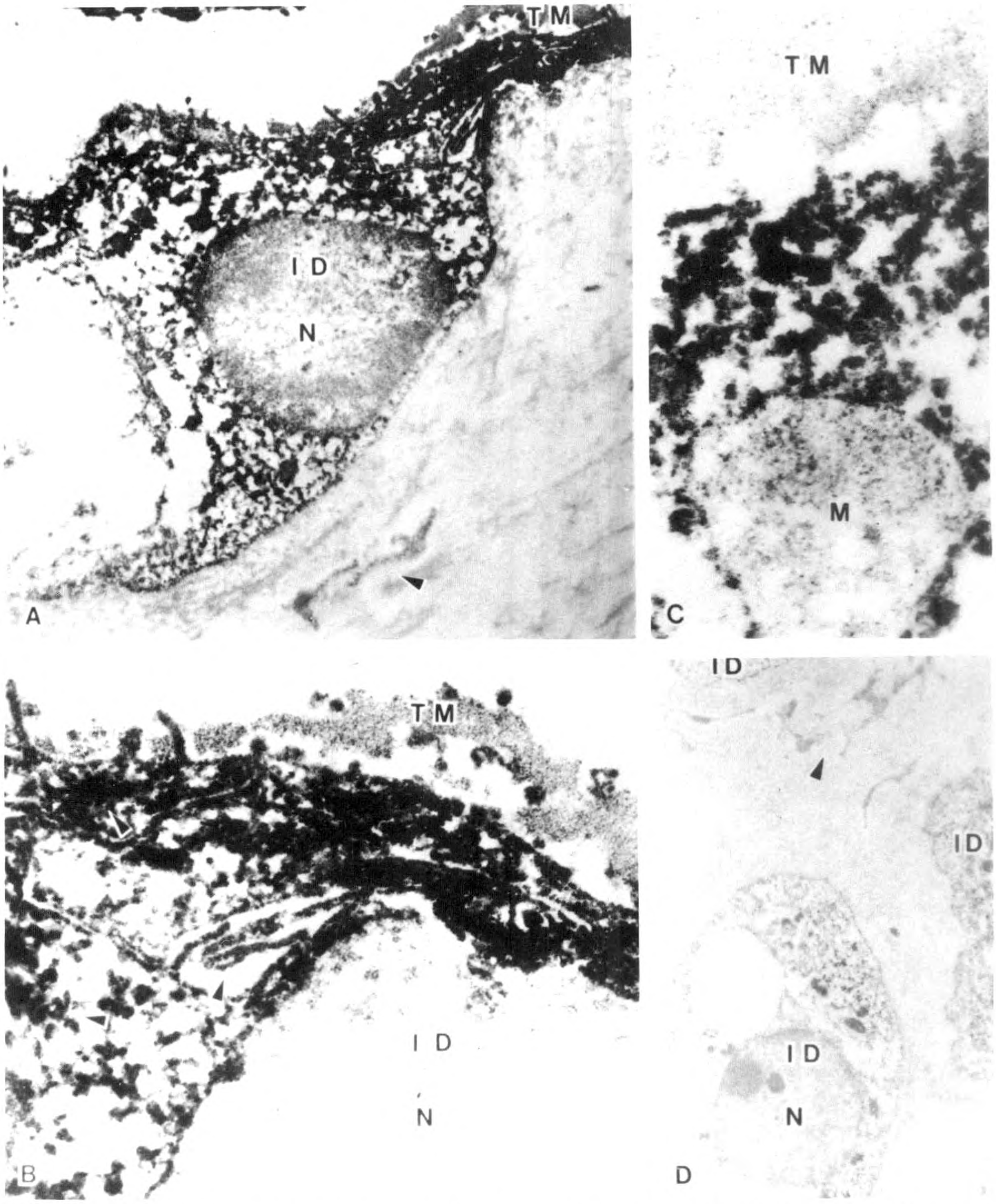

Fig 7. Immuno-electron microscopic localization of keratin in interdental cell (ID) of limbus by Triton X-100-treated pre-embedding method without counterstaining. N — nucleus. A) Abundant keratin-positive network in ID showing sharp border adjacent to connective tissue with few rootlet-like cytoplasm areas stained positively (arrowhead) (original x6,500). B) Higher magnification showing tubular structure (arrowheads) and close relationship with tectorial membrane (TM) (original x15,000). C) Fine granular network in ID (original x30,000). Note mitochondria (M) surrounded by NFKS. D) Horizontal section showing rootlet-like positive cytoplasm of ID in connective tissue (arrowhead) (original x3,000).

ing the biologic behavior of the NFKS might be postulated as follows.

1. The NFKS belongs to a highly specialized differentiation of epithelial cells in certain sensory organs such as the organ of Corti.

2. The NFKS appears to be involved in the secretion and absorption of endolymph and perilymph. Similar NFKS structures found in Reissner's membrane, Hensen's cells, spiral prominence cells, external sulcus cells, and interdental cells may be studied as an interesting approach to understanding the regulatory mechanisms for inner ear fluids. Both chemical and electrical gradients tend to move

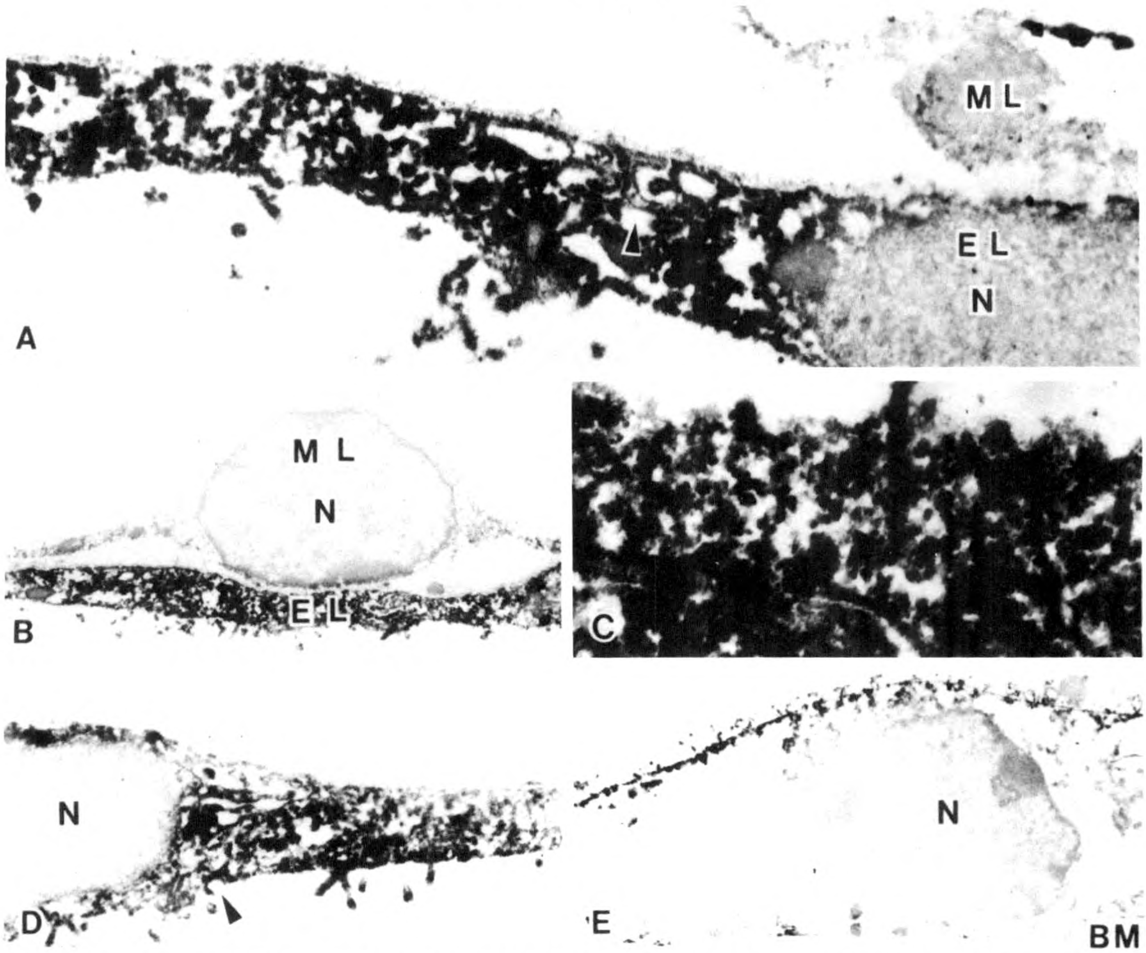

Fig 8. Immuno-electron microscopic localization of keratin in Reissner's membrane and inner sulcus cell by pre-embedding method without counterstaining. N — nucleus. A) Triton X-100-treated (original x10,000). Diffuse abundant keratin network in epithelial layer (EL) of Reissner's membrane showing tubular system (arrowhead). ML — mesothelial layer. B) Saponin-treated (original x3,000). EL of Reissner's membrane, showing strong positive staining to keratin but weak positive result in ML. C) Triton X-100-treated (original x6,500). Fine granular and filamentous network of NFKS in EL of Reissner's membrane (original x15,000). D) Tubular structure of NFKS in EL of Reissner's membrane (arrowhead). E) Triton X-100-treated (original x3,000). Keratin-positive staining in inner sulcus cell, mainly localized in apical region and with very weak reaction adjacent to basilar membrane (BM). Note BM stained negatively.

K^+ from cochlear endolymph into perilymph or the bloodstream. However, $^{42}K^+$ injected in the scala vestibuli enters the endolymph rapidly, and this may mean that Reissner's membrane provides a mechanism of active transport.[31] It was suggested that endolymph may be produced by exchange of inorganic ions across Reissner's membrane and by other tissues in the cochlear duct in addition to the stria vascularis.[32] The NFKS appearing in filamentous and tubular structures may provide a flexible architecture for maintaining the microhomeostasis of the inner ear fluids. A more interesting finding in this study was that most mitochondria in the supporting cells were surrounded by keratin-positive structures and that the NFKS formed a network connecting the cell membrane, cytoplasmic organelles, and nucleus (Fig 1). Therefore, the NFKS may have true cytoskeletal functions, including a secretory function through its involvement in cell surface cytoplasm-nucleus interactions.

3. The NFKS may play a role in intercellular communication in the organ of Corti.[33]

4. The characteristic structure of NFKS may provide a flexible functional system in the organ of Corti.

5. The NFKS may play a major role in separating endolymph from cortilymph or perilymph. Intercellular junctions in the organ of Corti have been extensively studied by means of the freeze-fracture method and electron microscopy.[34-38] It has been recognized that the junctional complexes between hair and supporting cells are much more extensive than those between extralaminar supporting cells, and that the endolymphatic junctional complex acts as a semipermeable barrier for the maintenance of inner ear ionic gradients. Keratin distribution in the organ of Corti examined by light microscopy showed clearly a strong positively stained "keratin curve" along the surface of the organ of Corti as previously reported.[39] Immuno-electron microscopic study has confirmed the presence of this curve. Presumably, keratin might play a role in sealing the

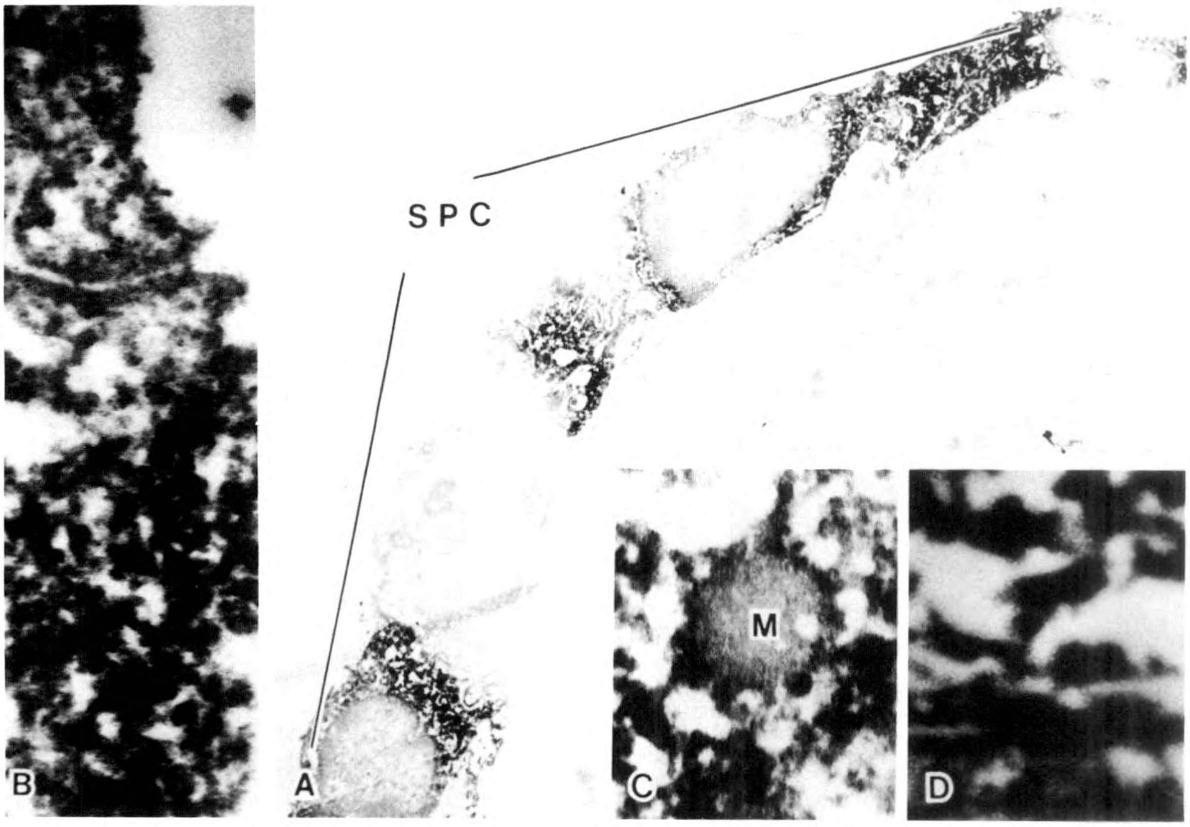

Fig 9. Immuno-electron microscopic localization of keratin in spiral prominence cell (SPC) and external sulcus cell by Triton X-100-treated pre-embedding method without counterstaining. A) SPC showing diffuse abundant keratin-positive network-appearing tubular system in cytoplasm (original x3,000). Note sharp border of SPC without cross-reaction in adjacent connective tissue. B) Higher magnification of same section showing tubular structure of SPC (original x30,000). C) Same section showing mitochondria (M) surrounded by NFKS (original x30,000). D) Similar structure of NFKS identified in external sulcus cell (original x30,000).

intercellular spaces of the organ of Corti. Gulley and Reese[35] demonstrated that the junctional patterns of extralaminar supporting cells such as Hensen's cells are typical of most epithelia and quite different from those in the RL. One may ask, how can the RL separate endolymph from cortilymph if Hensen's cells are not joined by the same tight junctions as found in the RL? One may find the answer by further studies based on a hypothesis that the keratin curve may be a chemical barrier existing in some cochlear supporting cells to play an important role in separating endolymph from cortilymph as a co-factor to the mechanical barrier (tight junction). Another example in support of this explanation is that Reissner's membrane separates endolymph from perilymph although it has the same structure as Hensen's cells.[6] Pathologic conditions may also influence the NFKS. It may be possible to demonstrate the first pathologic findings by keratin immunohistochemical study of the inner ear.

ACKNOWLEDGMENT — The authors thank Dr Tung-Tien Sun, New York University Medical Center, for kindly providing monoclonal keratin antibody.

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Ann Otol Rhinol Laryngol 99:1990

HISTOPATHOLOGIC STUDY OF OTITIS MEDIA IN INDIVIDUALS WITH HEAD AND NECK TUMORS

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Five temporal bones, each including the eustachian tube, were obtained from five adults with advanced malignant tumors of the head and neck. The specimens were from the side on which the tumor had occurred. Otitis media had been detected clinically in two cases, and was detected histopathologically in the other three. We discuss the possibility that otitis media might have been caused by tumor invasion of the paratubal area, by postoperative inflammation in the nasopharynx, or by an inflammatory reaction of tubal structures to radiotherapy, or that these conditions may have coexisted.

KEY WORDS — eustachian tube, head and neck tumor, histopathology, mastoid, middle ear, otitis media.

INTRODUCTION

Nasopharyngeal tumors are known to be accompanied often by hearing loss.[1-4] Otitis media has also been noted clinically in a significant number of patients with head and neck tumors (including tumors of the tonsil, soft palate, and maxillary sinus). In these cases the otitis media was assumed to be due to radiotherapy and surgical treatment.[5,6] Another possibility could be that these patients had undetected "silent" otitis media, to which clinicians should pay attention. However, these issues have not so far been thoroughly investigated because of the lack of histopathologic study in this field.

On the other hand, to date, most of the histopathologic studies on otitis media in general[7-11] have not dealt with investigating conditions of the eustachian tube. Thus, to obtain a better understanding of the pathogenesis of otitis media, and the eustachian tube's relationship to otitis media in patients with tumors of the head and neck, we studied five temporal bones that included the eustachian tube and its surrounding structures from individuals who had died of head and neck tumors. This paper reports the results of histopathologic studies of these specimens, and discusses factors that might have predisposed these ears to otitis media.

MATERIALS AND METHODS

Five adult temporal bone specimens that included the eustachian tube and its surrounding structures were removed, according to the method developed by us,[12] from five patients who had been treated at Eye and Ear Hospital of Pittsburgh for advanced malignant tumors of the head and neck. Temporal bone specimens were removed at autopsy from the side of the tumor, which in two cases was carcinoma of the tongue, in one was carcinoma of the oropharynx, in one was carcinoma of the alveolar ridge, and in the last case was lymphocytic lymphoma.[13]

The temporal bone specimens were processed for histologic study in a routine manner: they were fixed in 10% formalin, decalcified in 5% trichloroacetic acid, dehydrated in graded concentrations of ethanol, embedded in celloidin, and sectioned serially at 30 μm. The vertical sections were cut perpendicular to the long axis of the petrous bone, from the pharyngeal orifice of the eustachian tube to the mastoid air cells, and every 20th to 40th section was stained with hematoxylin and eosin.

The stained sections were evaluated by light microscopy. The middle ear–mastoid air cell system (epitympanum, mesotympanum, hypotympanum, promontory, oval window niche, round window niche, mastoid air cells, etc) and the eustachian tube and its accessory structures were studied.

RESULTS

The clinical and histopathologic findings are as follows.

CASE 1

This patient was a 68-year-old man who had car-

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Presented at the meeting of the American Academy of Otolaryngology–Head and Neck Surgery, Washington, DC, September 25-27, 1988.

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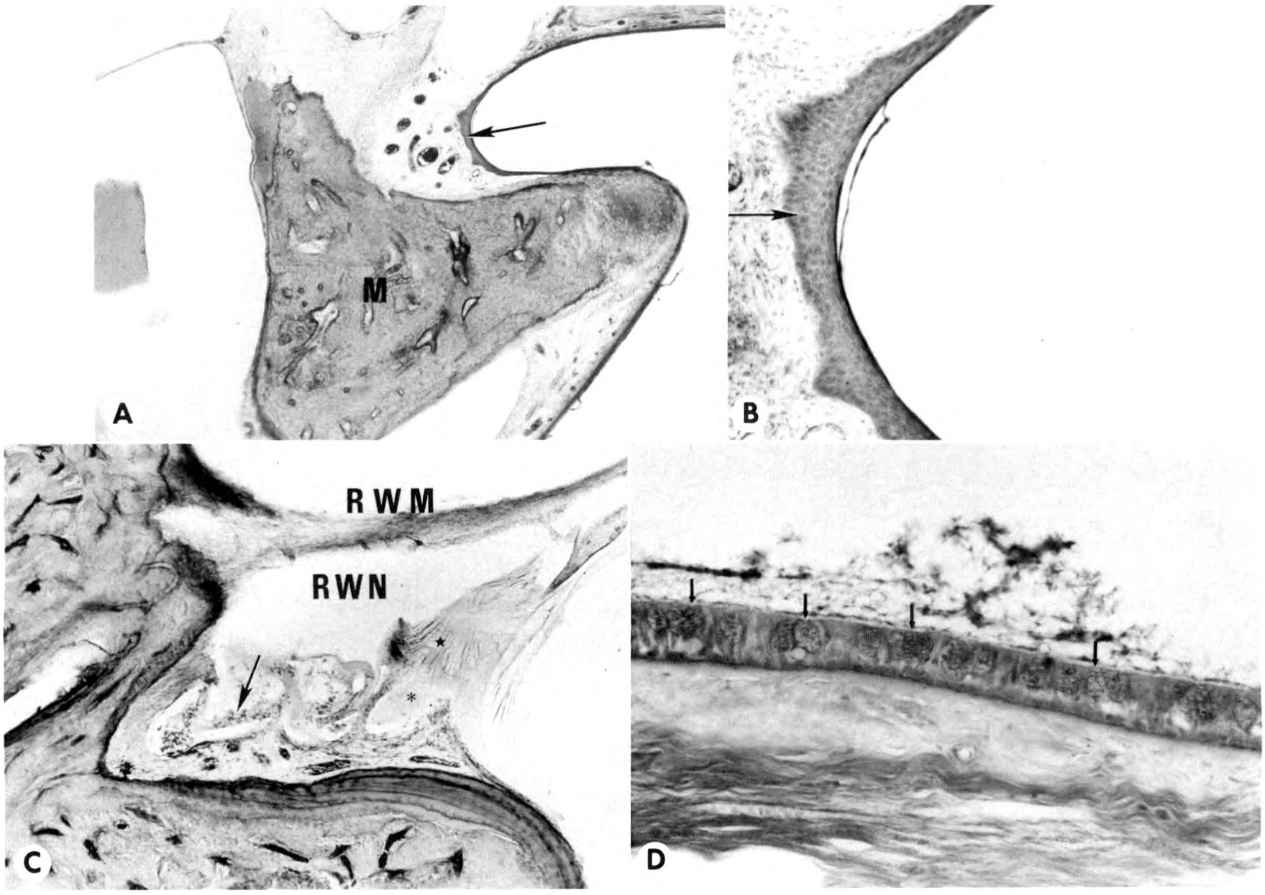

Fig 1. (Case 1) A,B) Retraction pocket seen in pars flaccida of tympanic membrane accompanied by acanthosis (arrows). Blood vessels had proliferated. A) Low-power view (H & E, original x20). M — malleus. B) High-power view (H & E, original x100). C) Fluid (asterisk) with fibrin (star) and macrophages (arrow) was present in round window niche (RWN) (H & E, original x40). Submucosal layer of niche was thickened and was infiltrated by mononuclear cells. RWM — round window membrane. D) Many goblet cells (arrows) were present in epithelium of eustachian tube (periodic acid-Schiff, original x200).

cinoma of the base of the tongue on the right (T3N3M0). Although this man had no history of ear disease or hearing loss, his audiogram obtained in January 1983 showed a mild bilateral sensorineural hearing loss (right ear: pure tone average [PTA], 28 dB; speech reception threshold [SRT], 28 dB). In March 1983, he underwent radiotherapy of 70 Gy to the right side of the oral cavity and 76 Gy to the right side of the neck. He died of acute bronchopneumonia and sepsis in June 1983, and the temporal bone was obtained 18 hours after death.

Histopathologic Findings (Right Ear). The pars flaccida of the tympanic membrane was retracted, and acanthosis was present (Fig 1A,B). Furthermore, blood vessels had proliferated in that portion of the ear.

Eosinophilic fluid and precipitates were present in all parts of the middle ear cavity. Fibrin was present in the round window niche (Fig 1C) and the oval window niche. Macrophages were present in the epitympanum, oval window niche, round window niche, hypotympanum, and mastoid air cells. Blood vessels in the submucosal layer of the epitympanum, promontory, oval window niche, and round window niche were dilated and had proliferated. The submucosal layer of the round window niche was conspicuously thickened (Fig 1C). Mononuclear cells had infiltrated the submucosal layer of the middle ear, which had become converted to fibrous connective tissue. The round window niche membrane was observed.

A large number of goblet cells were present in the midcartilaginous portion of the eustachian tube (Fig 1D). Proliferation of blood vessels and a small amount of mononuclear cells were notable in the submucosal layer.

CASE 2

This patient was a 70-year-old man who had carcinoma of the left alveolar ridge with an ulcer (T3N2M0). He had no history of ear disease. An audiogram obtained in June 1983 revealed a mild, bilateral, high-frequency hearing loss (left: PTA, 20 dB; SRT, 20 dB). He underwent a left segmental mandibulectomy, left radical neck dissection, and tracheostomy on June 22, 1983, but on the fifth postoperative day he died of a cardiac arrhythmia. The specimen was obtained 17 hours after death.

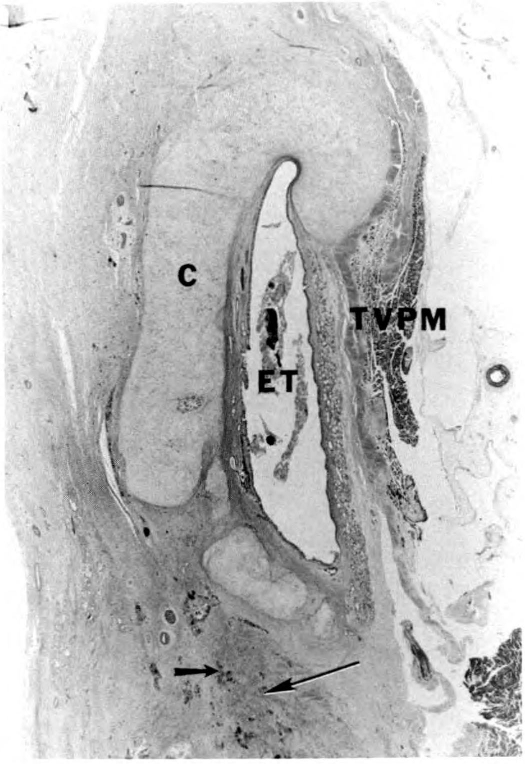

Fig 2. (Case 3) Levator veli palatini muscle replaced by fibrous connective tissue (long arrow) (H & E, original x20). C — eustachian tube cartilage, ET — eustachian tube, TVPM — tensor veli palatini muscle, short arrow — tumor cells in connective tissue.

Histopathologic Findings (Left Ear). The tympanic membrane showed proliferation and dilatation of blood vessels in the pars flaccida. The pars tensa was hypertrophic, thickened by fibrous connective tissue and cystic tissue.

Eosinophilic fluid and mononuclear cells were present in all parts of the middle ear cavity. Macrophages were present in the epitympanum, oval window niche, round window niche, hypotympanum, and mastoid air cells. There were many polymorphonuclear leukocytes in the hypotympanic air cells. Mononuclear cells had infiltrated the submucosal layer of all parts of the middle ear, and in particular many leukocytes and mononuclear cells had infiltrated the submucosal layer of the hypotympanum. The submucosal layer of the promontory was remarkably thickened. Blood vessels had proliferated in the round window niche membrane.

A large number of mononuclear cells were present in the submucosal layer of the midcartilaginous portion of the eustachian tube, and there were many more goblet cells than normal in the epithelial lining of the eustachian tube.

CASE 3

This patient was a 51-year-old man in whom an inoperative carcinoma of the left oropharynx (T4N2M0) was diagnosed in September 1981. He had no history of ear disease. The tumor extended from the level of the hyoid bone along the left lateral pharyngeal wall to the lateral wall of the nasopharynx. The patient underwent a tracheostomy and radiotherapy (48 Gy) to the oropharynx, then died of severe cachexia and bronchopneumonia in October 1981. The specimen was obtained 17 hours after death.

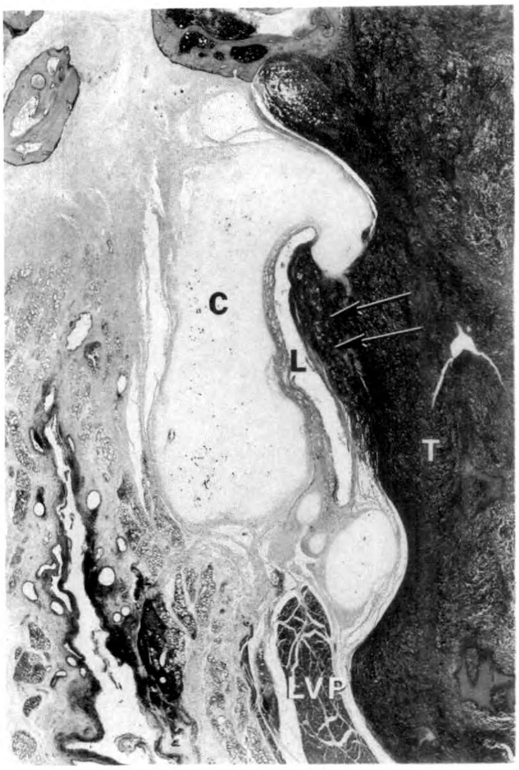

Fig 3. (Case 4) Vertical section of midcartilaginous portion of left eustachian tube (H & E, original x12). Tensor veli palatini muscle is completely destroyed by tumor cells (T). Levator veli palatini muscle (LVP) is compressed by tumor medially, but tubal lumen (L) is still open. Only tendon of tensor veli palatini muscle and surrounding connective tissue (arrows) remain intact. C — tubal cartilage.

Histopathologic Findings (Left Ear). The tympanic membrane was normal. Eosinophilic fluid and macrophages were present in the hypotympanum and mastoid air cells, and a few mononuclear cells were present in the lumen and the submucosal layer of the epitympanum.

A large number of goblet cells were present in the epithelium of the midcartilaginous portion of the eustachian tube. Squamous cell carcinoma had invaded the submucosal layer of the eustachian tube between the pharyngeal portion and the isthmus, and mononuclear cells and keratohyalin were present in the submucosal layer of the eustachian tube. Keratohyalin, mononuclear cells, and giant cells were also present in the area medial and inferior to the eustachian tube cartilage. The tensor veli palatini (TVP) muscle was normal, but part of the leva-

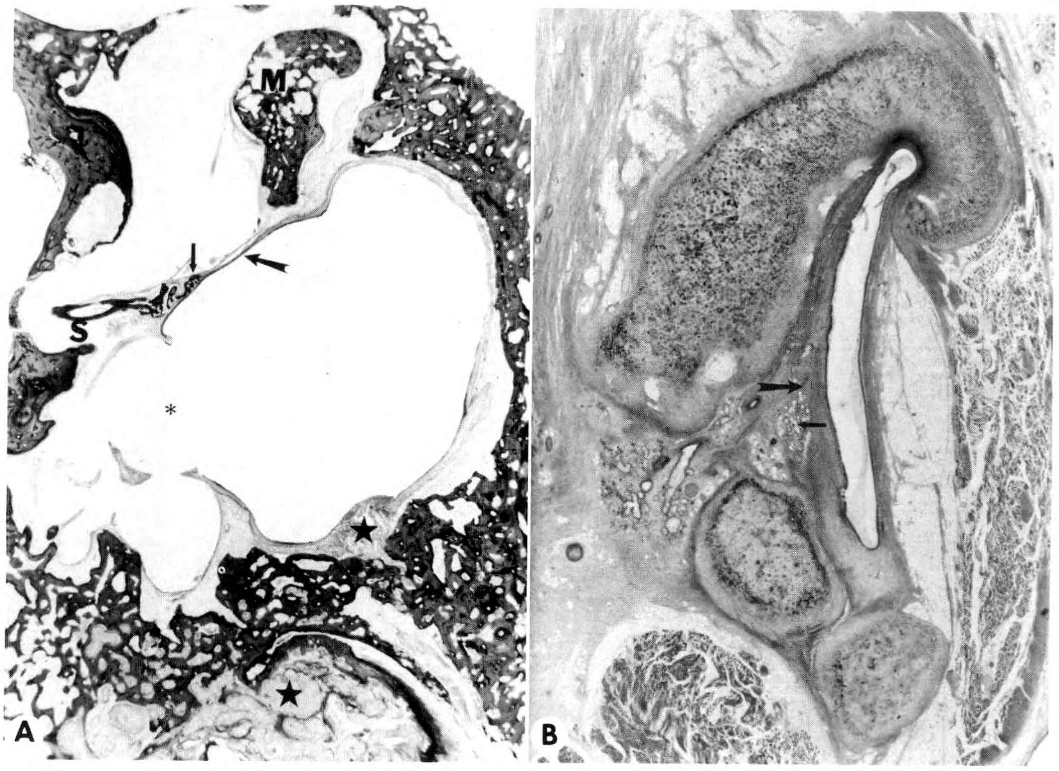

Fig 4. (Case 5) A) Pars tensa (large arrow) of tympanic membrane was retracted, thickened (especially its epidermal layer), and partially perforated (asterisk) (H & E, original x28). Lenticular process of incus (small arrow) was attached to retracted membrane (myringoincudopexy). Tumor (stars) had invaded subepithelial layer of external ear and bone marrow. M — malleus, S — stapes. B) Glands in submucosal layer of eustachian tube had been replaced by dense fibrous connective tissue (large arrow) and fat (small arrow) (H & E, original x28).

tor veli palatini (LVP) muscle had been replaced by fibrous connective tissue (Fig 2). Tumor cells were scattered in this tissue.

CASE 4

This patient was a 26-year-old man with undifferentiated lymphocytic lymphoma diagnosed by biopsy of the mediastinum in October 1980. He received chemotherapy (Cytoxan, Adriamycin, Oncovin, prednisone, and bleomycin sulfate) and radiotherapy (30 Gy) in May 1981. In August 1981, a mass below the right ear was noted and treated by radiotherapy (25 Gy). An audiogram obtained 1 month before death showed conductive hearing loss (left: PTA, 40 dB; SRT, 50 dB). A left facial palsy and bilateral otitis media with effusion appeared in September 1981. The man died in October 1981, and the left temporal bone was obtained 16 hours after death.

Histopathologic Findings (Left Ear). A middle ear effusion containing macrophages was present in all parts of the middle ear cavity. Mononuclear cell infiltration of the submucosal layer had occurred, and blood vessels had proliferated in all parts of the middle ear cavity.

Tumor had invaded the submucosal layer of the cartilaginous portion of the eustachian tube. The posterior part of the TVP muscle had been destroyed, and the LVP muscle had been compressed medially by the tumor. There were many goblet cells in the epithelium of the eustachian tube. Mononuclear cells were present in the submucosal layer of the eustachian tube (Fig 3).

CASE 5

This patient was a 71-year-old woman with advanced poorly differentiated carcinoma of the tongue and right tonsil (T4N2M0). She was treated with chemotherapy (methotrexate) from 1974 to 1979 and radiotherapy (75 Gy) to the base of the tongue and the neck in 1974. In 1977, the tumor recurred in the right upper posterior part of the neck and was treated with radium needle implants (50 Gy). In January 1980, she developed a right peripheral facial palsy and was again treated with external irradiation of the mastoid area (28 Gy). An audiogram obtained in January 1980 showed bilateral sensorineural hearing loss (PTA, 30 dB; SRT, 28 dB). In June 1980, she received a course of cisplatin for the recurrent tumor of the right side of the neck, and tympanostomy and tube insertion for the otitis media with effusion in her right ear. She died of bleeding due to the tumor in September 1980. The temporal bone specimen was obtained 9 hours after death.

Histopathologic Findings (Right Ear). The tumor had invaded the subepithelial layer of the posteroinferior region of the external ear near the tympanic membrane and the bone marrow in the mastoid portion of the temporal bone (Fig 4A). The pars tensa of the tympanic membrane was hypertrophic, retracted, and adherent to the lenticular process of the incus; perforation of the eardrum was also evident (Fig 4A).

Signs of a chronic otitis media with acute recurrence were present. Eosinophilic fluid and fibrin were present in all parts of the middle ear cavity, and macrophages were present in the epitympanum, oval window niche, and round window niche. Polymorphonuclear cells were present in the hypotympanic space, and a moderate amount of desquamated debris (epidermal and squamous epithelial cells) was present in the middle ear cavity. The submucosal layer of the round window niche and the promontory was distinctly thickened and fibrotic, and mononuclear cells had infiltrated the submucosal layer of the hypotympanum to a remarkable extent.

Carcinoma cells were seen in the facial nerve, the chorda tympani, and the stapedius muscle (mastoid portion).

Mononuclear cells were conspicuous in the submucosal layer of the eustachian tube, as were many goblet cells. The glands in the submucosal layer of the eustachian tube were decreased in number; most of these glands had been replaced by dense connective tissue or fat (Fig 4B).

DISCUSSION

Several papers have reported on otitis media with effusion in patients with tumors of the head and neck. Myers et al[5] reported that the incidence of otitis media with effusion after head and neck operations was high in particular in patients who had undergone total maxillectomy and total soft palate resection with ablation of the TVP muscle. Brill et al[6] reported that radical neck dissection is sometimes complicated by the lymph retention due to interruption of lymphatic drainage. Otitis media sometimes has been noted to occur during or after radiotherapy for head and neck tumors[14,15]; Moss[16] called this "radiation otitis media" and reported that clinically it was characterized by edema of the mucosa and a collection of "sterile fluid" in the middle ear after irradiation.

These reports seem to show that more than one factor may predispose patients with head and neck tumors to otitis media with effusion. The following discussion focuses on those factors in the pathogenesis of otitis media that relate to the eustachian tube.

1. Inflammation of the nasopharynx after extirpation of an oral cavity tumor and reconstruction of the oral cavity may lead to extensive inflammation in the middle ear and eustachian tube, as in case 2.

2. Interference with lymphatic drainage as a result of local tissue resection and radical neck dissection may also play a role in the development or prolongation of otitis media with effusion.

3. Radiotherapy to the head and neck (cases 1, 3, and 5) may cause inflammatory changes in the middle ear and eustachian tube. In the early stage, middle ear inflammation may occur if radiotherapy causes mechanical obstruction of the eustachian tube, as is thought to have happened in cases 1 and 3. In the late stage, radiotherapy to the upper posterior neck may cause chronic dysfunction of the eustachian tube as the result of dense fibrous connective tissue's gradually replacing inflamed submucosal tissue (case 5). In case 5, the radiotherapy to the mastoid area may have further promoted the otitis media.

4. As happened in case 4, destruction by invading tumor of the TVP muscle near the eustachian tube, ie, functional obstruction of the eustachian tube, may produce severe otitis media with effusion. In case 3, the LVP muscle in the area inferior to the eustachian tube was invaded by tumor, but the otitis media that was present was not so severe as in case 4. This difference in severity of otitis media may have to do with the functions of the two muscles involved: the TVP muscle causes direct opening of the eustachian tube,[17,18] whereas the LVP muscle possibly causes indirect opening by elevating the floor of the tube.[19]

It has been reported that the number of goblet cells increases when otitis media is present[11,20,21] and also that acute catarrhal infection of the eustachian tube is associated with increased mucin in the goblet cells.[22] The presence of increased numbers of goblet cells in the eustachian tubes in our five cases helps to confirm that persistent inflammation exists in the eustachian tubes of patients with tumors of the head and neck. This makes it likely that the tumor is an important factor predisposing to otitis media with effusion.

In this study, fluid and inflammatory cells were noted in the middle ear and the eustachian tube in all five cases, although otitis media was clinically detectable in only two of them. The remaining three patients (cases 1, 2, and 3) were considered to have silent otitis media, a quiet chronic pathologic condition of the middle ear reported by Paparella et al,[7] although the otitis media in case 1 might have existed before tumor invasion and might have been exacerbated by the tumor invasion. This suggests that patients with head and neck tumors, even those with normal tympanic membranes, may have silent otitis media. Therefore, clinicians should be aware that otitis media often follows invasion of tumor into the area of the eustachian tube and treatment of advanced tumors of the head and neck by surgery and radiotherapy, and should evaluate such patients for this pathologic condition.

Of the four patients who had had audiometry, three had sensorineural hearing losses only, without the conductive loss that usually accompanies otitis media. We believe conductive hearing losses could not be detected in cases 1 and 5 at audiometry, but that during the considerable time lag between audiometric testing and the patients' deaths, their otitis media may have progressed. In case 2, although the audiogram was obtained within a month of the patient's death, the extensive operation on the patient's mandible and neck that was performed after audiometry undoubtedly affected the eustachian tube and middle ear and aggravated this patient's otitis. These three patients, then, probably had such mild otitis at the time of audiometry that it was not detected on the audiogram, while the case 4 patient had had audiometry very soon before death and had not had any experience that would have been expected to change his conductive hearing from that measured on the audiogram. This patient's audiogram, which showed considerable conductive hearing loss, is therefore considered to reflect a true picture of his otitis.

Histopathologic studies of additional temporal bone specimens that include the eustachian tube obtained from patients with head and neck tumors will be performed to confirm these findings.

ACKNOWLEDGMENTS — The authors thank Charles D. Bluestone, MD, Professor and Director of the Pediatric Otolaryngology Division and Otitis Media Research Center, University of Pittsburgh School of Medicine, and Jonas Johnson, MD, Professor, Department of Otolaryngology, University of Pittsburgh School of Medicine, for encouraging them to continue this project and for offering helpful criticism. Appreciation is also given to Karen Milligan for her kind assistance.

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IMAGING CASE STUDY OF THE MONTH

INTERNAL AUDITORY CANAL ENLARGEMENT IN PAGET'S DISEASE APPEARING AS BILATERAL ACOUSTIC NEUROMAS

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A 69-year-old man with a past history of bladder cancer was seen for the evaluation of chronic headaches and recent onset of bilateral hearing loss that was worse on the left. Left-sided cluster headaches had been present for years. More recently the headache had been bilateral-frontal in location and did not decrease with medication. The hearing loss was present for 6 months. On testing it was found to be a mixed conductive and sensorineural loss.

RADIOGRAPHIC FINDINGS

During initial evaluation, a magnetic resonance scan was performed. An axial T2-weighted image showed intense signal arising from the intracanalicular portions of the acoustic nerves bilaterally (Fig 1). Mottled signal of the diploic space in the skull base was also found, as well as basilar invagination on a sagittal view. Provisional diagnoses were probable bilateral acoustic neuromas and Paget's disease of the skull base.

To further evaluate the extent of intracanalicular masses and possible involvement of the cochlear apparatus by Paget's disease, a computed tomographic (CT) air-contrast cisternogram was performed (Fig 2). The internal auditory canals were enlarged to 10 mm bilaterally without evidence of any space-occupying lesion. Decreased mineral content with marrow expansion was also shown within the temporal bone, although the cochlear apparatus appeared intact.

Clinical follow-up 2 months later revealed continuing hearing loss despite the institution of bilateral hearing aids. The patient's headaches persisted, explained only on the basis of Paget's disease involvement of the skull.

DISCUSSION

Paget's disease (osteitis deformans) is a heritable condition with a prevalence of 3% in the population over age 40. The skull is involved in up to 70% of cases. Cranial nerve impairment is common, with loss of hearing reported to be the most frequent (30% to 50% of those with skull involvement).[1]

Microscopically, the disease is characterized by simultaneous processes of osteoclastic resorption and osteoblastic repair. The marrow space is replaced by cellular infiltration and fibrosis. Within the temporal bone, the process begins in the marrow-rich petrous pyramids and extends in advanced stages to the marrowless compact bone of the otic capsule.[2] The resultant softening of the skull base and petrous pyramids leads to upward rotation of the petrous apices and basilar invagination, both easily demonstrated by polytomography.[1]

Hearing loss in Paget's disease is usually of the sen-

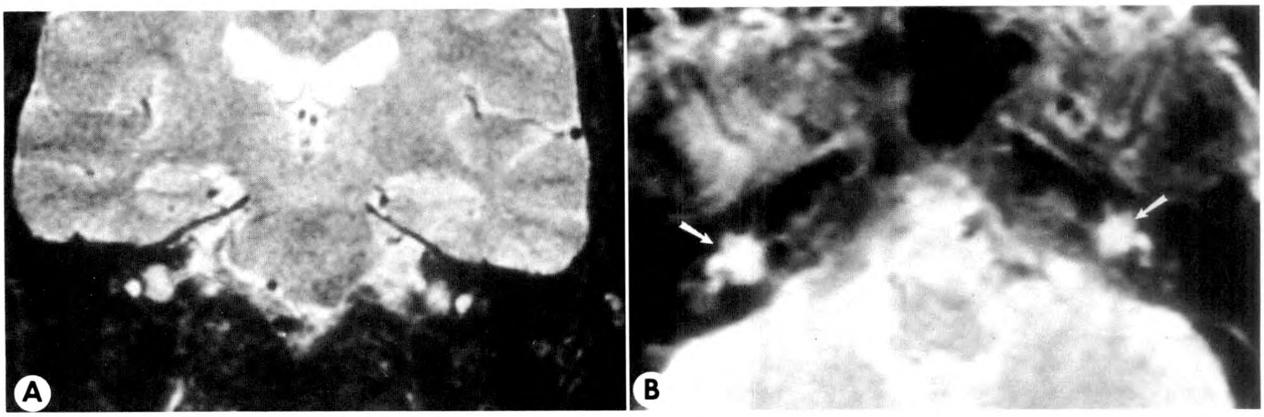

Fig 1. T2-weighted magnetic resonance imaging. A) Bilateral internal canal enlargement on coronal view. B) Detail axial view with enlarged canals at arrows.

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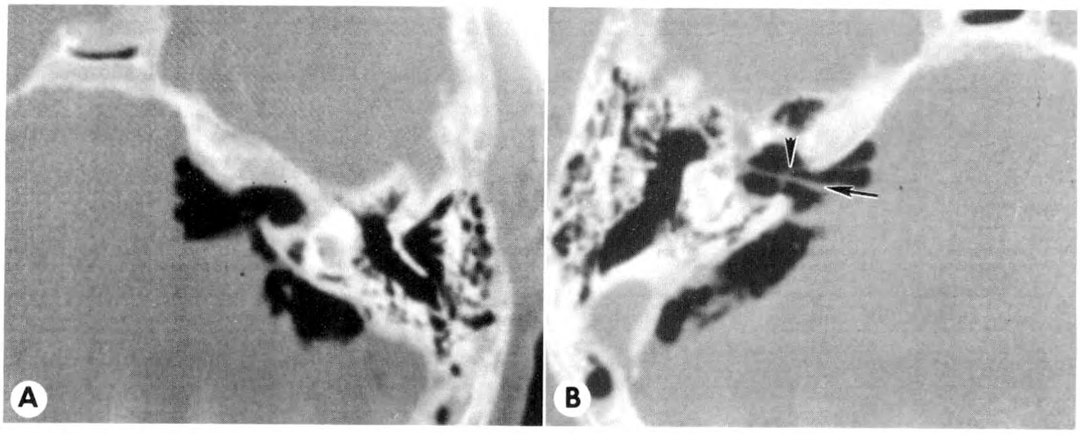

Fig 2. Air cisternogram studies. A) Left side with enlarged internal auditory canal lateral to porus acusticus. B) Right side with similar internal auditory canal enlargement lateral to porus acusticus. Arrow — nerve trunk, arrowhead — intracanalicular vascular loop at point of nerve contact.

sorineural or mixed type. No consensus regarding the pathogenesis of hearing loss has been reached; proposed mechanisms include labyrinthine microfractures, arteriovenous shunts, labyrinthine toxins, stretching of cranial nerves with the remodeling of bone, and cranial nerve impingement by new bone deposition in the internal auditory canal.[1,3-5]

In our patient the nerve trunk was normal in size on the left side (not illustrated). On the right the nerve trunk was small in size and a vascular loop was visualized adjacent to the trunk, but did not compress the nerve (Fig 2B).

Relatively few reports have documented canal narrowing of significant enough degree to yield nerve compression.[3,4,6] On the other hand, we are aware of only one histopathologic description of internal auditory canal enlargement by Paget's disease.[7]

The current case presents an interesting dilemma in differential diagnosis. Concurrent temporal bone Paget's disease and internal auditory canal tumors were considered, and this combination has been reported. Nager[1] found intracanalicular tumors in four of eight patients with temporal bone osteitis deformans. These tumors included neuromas, a fibroma, and a spindle cell sarcoma. Lindsay and Suga[4] and Page[8] have reported on acoustic neuromas in patients with temporal bone Paget's disease. The finding of bilateral cranial nerve tumors in the setting of Paget's disease is not unique, with a case of bilateral neurofibromas reported by Proops et al.[5]

On the other hand, widening of internal auditory canals in Paget's disease in the absence of intracanalicular tumor has been reported only once and without radiographic correlation.[7] Previous reviews of polytomography presented by Petasnick[2] and Davies[7] point out that it becomes impossible to identify the canal as a distinct structure and to assess canal size radiographically when temporal bone involvement is extensive in Paget's disease. Thus, it is possible that previous radiographic series have not detected cases of canal enlargement. Lack of reported cases in histopathologic and more recent CT literature nonetheless indicates that few cases of canal expansion are encountered.

The present case is interesting in that the signal appearance of normal cerebrospinal fluid in abnormally dilated internal auditory canals was indistinguishable from the abnormal signal seen with intracanalicular tumor. As the cause of canal widening was not certain on unenhanced CT, the diagnosis could only be made with an air-contrast CT study of the temporal bones and internal auditory canals. Gadolinium-enhanced magnetic resonance imaging may be of help in more accurately assessing the presence of acoustic neuroma in such a case. It was not available to us at the time this patient was studied.

We postulate that the internal canal enlargement was produced by the effect of pulsating cerebrospinal fluid on the pagetoid bone lining the internal canal, since the normal cortical bone around the porus acusticus was not affected.

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PATHOLOGY CONSULTATION

HISTOPATHOLOGIC GRADING OF SALIVARY GLAND NEOPLASMS: I. MUCOEPIDERMOID CARCINOMAS

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Histopathologic grading of salivary gland neoplasms has been done with various degrees of success and hence various degrees of acceptance among pathologists and otolaryngologists–head and neck surgeons. Given their histopathologic diversity, three carcinomas — mucoepidermoid, adenoid cystic, and acinic cell — would seem to be suitable candidates for grading. In this, the first of a three-part series, the authors present a three-level grading scheme for mucoepidermoid carcinomas. It combines histocytologic and growth features of the carcinomas that independently or together, in other grading proposals, have shown prognostic value.

Originally intended to subjectively convey the degree of differentiation of a neoplasm, histopathologic grading of malignancies is now employed to provide one of several variables considered useful in the assessment of biologic aggressiveness, response to therapy, and prognosis. The grade of a neoplasm is usually expressed in either numeric terms (1, 2, 3) or descriptively (well, moderately, or poorly differentiated). In some instances, adjectival descriptors alone serve the grading function, eg, myxoid liposarcoma, papillary thyroid carcinomas.

Grading of salivary gland carcinomas has never had the acceptance or the degree of transferability to biologic activity credited to grading of other malignancies, eg, squamous cell carcinomas or sarcomas. Their relatively low incidence, numerous subtypes, and mandatory long follow-up periods may be the principal impediments, but lack of definition of the grading constituents is also responsible. It is also clear that grading subserves clinical stage and thoroughness of the primary surgical excision in nearly every instance.[1,2] For some salivary carcinomas, the classification itself implies the grade. The salivary duct carcinoma, for example, is a high-grade malignancy, as amply evinced by its high lethality.[3] The terminal duct adenocarcinoma of the palate, on the other hand, is biologically low-grade with a very low mortality.[4]

Because they have a broader range of phenotypic expression and also biologic aggressiveness, mucoepidermoid, adenoid cystic, and acinic cell carcinomas would seem to be ideal candidates for an acceptable transfer of grade to biologic course. The following presents the status of and a proposal for the histopathologic grading of mucoepidermoid carcinomas.

Mucoepidermoid carcinomas are basically composed of three cell types: mucin-secreting, epidermoid, and intermediate. The intermediate cell is well named, since it is likely the progenitor of the two other cells (Fig 1). It should also be appreciated that "epidermoid" is not synonomous with squamous, and its use is adjectival to signify squamous-like. Individual cell keratinization and certainly the development of keratin pearls are rarely seen in any mucoepidermoid carcinoma. Should they be prominent, mucoepidermoid carcinoma is unlikely.

There is considerable variation in cell types, distribution of cells, and their growth pattern in the carcinomas. The histopathologic appearance of a mucoepidermoid carcinoma is the result of the interplay of the variations, with the cells arranging themselves in cystic or glandular structures, solid nests or cords, or combinations of these architectural displays. A chronic inflammatory cell reaction with or without fibrosis is often seen. If the neoplastic cells are well differentiated and cystic changes prominent, the chronic inflammation may suggest a sialadenitis with ductal metaplasia and ectasia. The sclerosing mucoepidermoid carcinoma epitomizes the pronounced hyalinization and fibrosis that can occur in mucoepidermoid carcinomas (Fig 2). None of the carcinomas are encapsulated, and while

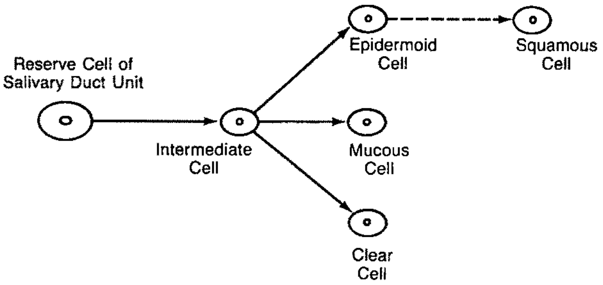

Fig 1. Suggested histogenesis of mucoepidermoid carcinoma. In this scheme, intermediate cell is progenitor, through differentiation, for all other light microscopic phenotypes of mucoepidermoid carcinomas.

From the University of Texas M. D. Anderson Cancer Center, Houston, Texas.

REPRINTS — John G. Batsakis, MD, Dept of Pathology, University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Blvd, Houston, TX 77030.

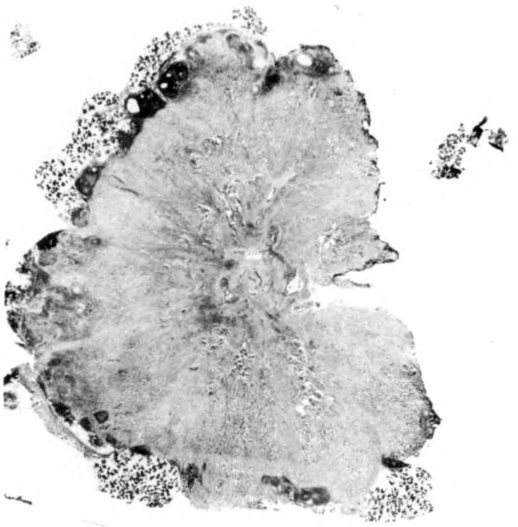

Fig 2. Sclerosing mucoepidermoid carcinoma of parotid gland (H & E, original x15). Only islands of histologically low-grade carcinomas are visible in this extensively hyalosclerotic neoplasm.

nearly all convey an infiltrative quality, some may be circumscribed.

That there is no uniformly accepted grading system for mucoepidermoid carcinomas despite nearly half a century of trying is testimony to 1) a lack of consensus as to what features should be used to formulate the grades and 2) an imperfect separation of grade, as an independent prognostic variable, from the size of the neoplasm and its clinical stage. It must also be understood that grading cannot substitute for appropriate histopathologic classification. In that light, the circumscribing of a classification to only those mucoepidermoid carcinomas that are easily recognized distorts the clinical implications of grading.

The first attempt at grading of mucoepidermoid carcinomas led to a division into two groups: qualified benign (relatively favorable) and qualified malignant (highly unfavorable).[5] The authors of this adventitious scheme, Foote and Frazell,[6] noting the arbitrary nature of this type of grading and also that some of their "benign lesions" had metastasized, concluded that all mucoepidermoid tumors were malignant, albeit in degrees: low, intermediate, and high grades.

Three-level grading found general acceptance among pathologists, and differences in biologic behavior could be demonstrated even though clinical stage became the better prognosticator. Predictably, however, attacks on the three grades have been mounted. Some investigators place their emphasis on cellular characteristics, eg, level of differentiation, pleomorphism of cells, nuclear irregularities, number of mitoses.[7,8] Others eschew such cytologic features and rely on growth patterns such as solid or cystic and "invasion."[9,10] Jakobsson et al[10] determined grade solely from the presence or absence of "invasive growth," a quality neither defined nor well illustrated in their report. Indeed, unencapsulated carcinomas, especially those with an origin from ramifying ducts, possess an invasive appearance even though their cytologic features are rather banal. Evans,[9] studying an ellipsis of mucoepidermoid carcinomas, also ignored cell types and differentiation to declare high-grade carcinomas to be those with a greater than 90% solid architecture. All others are low-grade.

Despite the observations from multivariate analyses that clinical stage at the time of diagnosis is the most important prognostic variable, the histologic features of salivary gland carcinomas are also independent factors that bear on patient outcome.[2,11,12] The trend to use only two grades (high and low) for mucoepidermoid carcinomas ignores the prognostic differences shown by authors who have used a three-tiered scheme. The 6%, 20%, and 78% recurrence rates for grades 1, 2, and 3, respectively, reported by Healey et al[1] are very similar to those reported by others. Spiro et al,[13] in 1978, found that 5-year determinate cure rates were 92%, 83%, and

GRADES OF MUCOEPIDERMOID CARCINOMAS AND THEIR HISTOCYTOLOGIC CHARACTERISTICS

Grade 1 (Low)	*Grade 2 (Intermediate)*	*Grade 3 (High)*
Macrocysts and microcysts; transitions with excretory ducts	No macrocysts; fewer microcysts; solid nests of cells	No macrocysts; preponderantly solid, but may be nearly all microcystic glandular
Differentiated mucin-producing cells and epidermoid cells, often in a 1:1 ratio; intermediate cell population minimal to moderate (focal)	Intermediate cell preponderance with or without epidermoid differentiation; mucin-producing cells may be sparse	Differentiated cells difficult to find, especially mucin-positive cells
Daughter cyst proliferation from larger cysts	Large duct population far less conspicuous	Cell constituents range from poorly differentiated to recognizable epidermoid and intermediate to ductal-type adenocarcinoma with epidermoid and intermediate cell participation
Minimal to absent pleomorphism and rare mitoses	Slight to moderate pleomorphism; few mitoses; nuclei and nucleoli more prominent	Considerable pleomorphism; prominent nucleoli; easily found mitoses
Broad-front, often circumscribed invasion	Invasive quality usually well defined and uncircumscribed	Unquestioned invasion: soft tissue, perineurial, and intravascular
Pools of extravasated mucin with stromal reaction (eg, fibrosis, chronic inflammatory cells)	Chronic inflammation at periphery; fibrosis separates nests of cells and groups of nests	Chronic inflammation less prominent; desmoplasia of stroma may outline invasive clusters

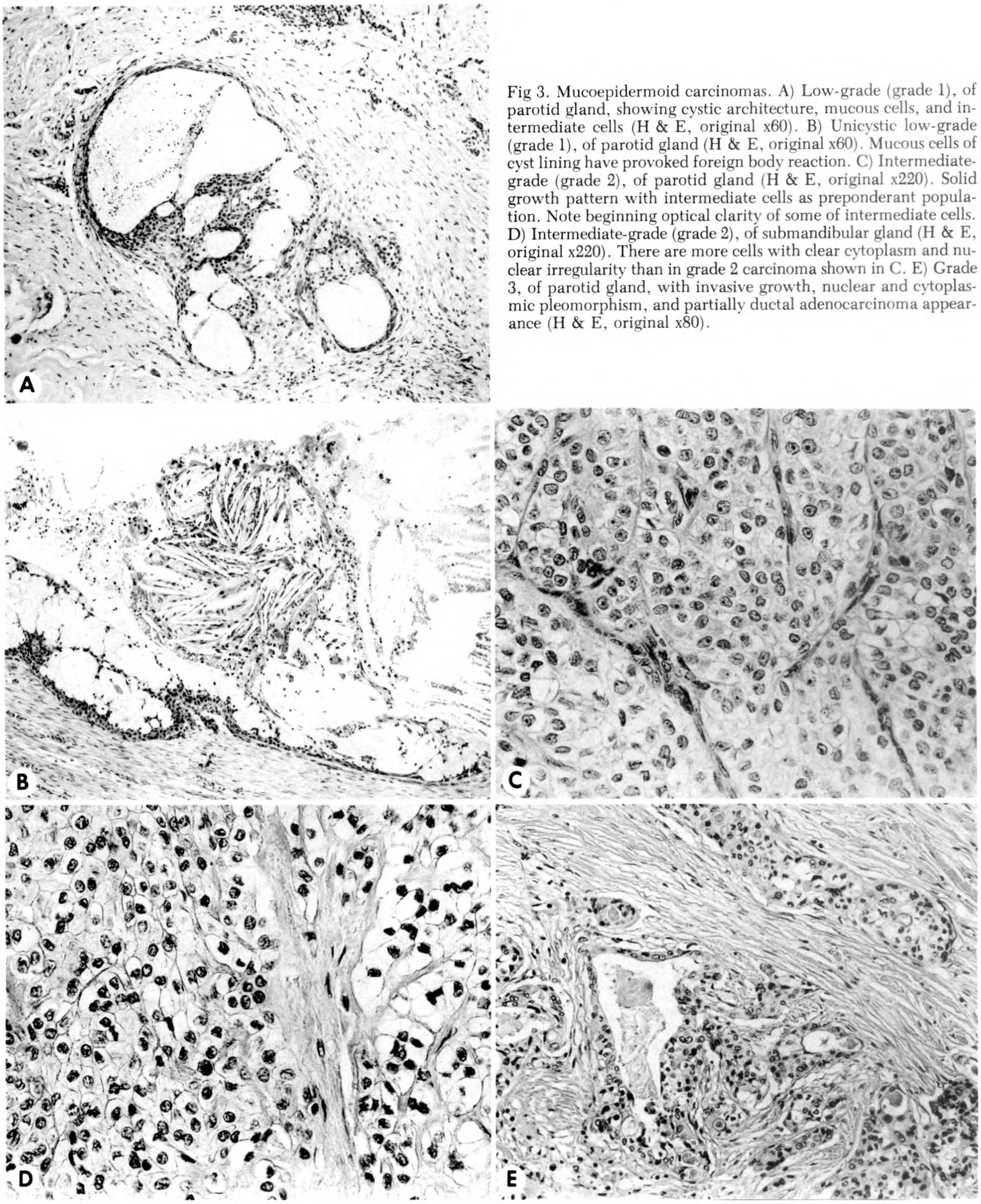

Fig 3. Mucoepidermoid carcinomas. A) Low-grade (grade 1), of parotid gland, showing cystic architecture, mucous cells, and intermediate cells (H & E, original x60). B) Unicystic low-grade (grade 1), of parotid gland (H & E, original x60). Mucous cells of cyst lining have provoked foreign body reaction. C) Intermediate-grade (grade 2), of parotid gland (H & E, original x220). Solid growth pattern with intermediate cells as preponderant population. Note beginning optical clarity of some of intermediate cells. D) Intermediate-grade (grade 2), of submandibular gland (H & E, original x220). There are more cells with clear cytoplasm and nuclear irregularity than in grade 2 carcinoma shown in C. E) Grade 3, of parotid gland, with invasive growth, nuclear and cytoplasmic pleomorphism, and partially ductal adenocarcinoma appearance (H & E, original x80).

27% for histologically low-grade, intermediate-grade, and high-grade carcinomas, respectively. Thorvaldsson et al[7] concluded that while all mucoepidermoid carcinomas were locally invasive and could recur after operation, distant metastases and death were very unlikely in patients with grade 1 and 2 carcinomas. By contrast, grade 3 carcinomas were fatal in a large percentage of cases, for a 5-year survival rate of 42%.

A three-level grading system modeled after the one proposed by Healey et al[1] forms a concinnity and is presented in the Table. It incorporates cytodifferentiation as well as growth patterns, emphasizes the intermediate cell population as an integral histogenetic and histologic component, and recognizes poorly differentiated types of the carcinomas[1,14] (Fig 3). With increasing grade, there is less cytodifferentiation, less mucicarminophilism, greater cellular pleomorphism and other cytologic signs of histologic malignancy, more invasive features, and a solid rather than cystic architecture. Although mucoepidermoid carcinomas are divisible into three grades, there is a continuum, at the beginning and end of which are the two extremes in appearance. The distinction of some low-grade carcinomas from an inflammatory-based sialadenitis may rely on the finding of daughter cyst proliferations from a seemingly hyperplastic duct. High-grade carcinomas show a preponderantly solid ductal or poorly differentiated cytoarchitecture, are unequivocally histologically malignant, and betray their lineage as mucoepidermoid carcinomas by foci of intermediate and epidermoid cells.

Are more objective pathologic assessments of the carcinomas helpful in creating a prognostic formula? Immunophenotyping of the epithelial cells and histochemical study of their mucins have not been.[15] The carcinomas are capable of producing a very heterogeneous population of epithelial mucins and there is no distinctive, monospecific staining characteristic that can be correlated with histologic grade. It is evident, however, that intracellular mucin becomes more difficult to demonstrate with increase in grade. Most well-differentiated mucoepidermoid carcinomas have a cytophotometric single cell DNA content in the diploid to tetraploid range with a diploid or near-diploid mode, not unlike pleomorphic adenomas.[16,17] An atypical DNA histogram usually means an unfavorable course, regardless of the histologic grade, but diploidy does not necessarily imply a good clinical outlook.

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OBITUARY

DAVID D. DEWEESE, 1913-1990

David D. DeWeese, MD, Professor Emeritus, Department of Otolaryngology, University of Oregon Medical School, Portland, died on March 1, 1990.

Dr DeWeese was born in Columbus, Ohio, March 16, 1913. He attended various elementary and secondary schools in Ohio, graduated from the University of Michigan, Ann Arbor, in 1934, and received his MD degree from the same institution in 1938. He served his residency in Michigan also, spending 2 years in the Department of Surgery and 4 years in the Department of Otolaryngology. He taught in the Department of Otolaryngology for 2 years, and in 1946 he moved to Portland, Oregon, and joined the Portland Clinic. He was also appointed Clinical Professor of Otolaryngology at the University of Oregon Medical School. After a successful period of time at the Portland Clinic, he was appointed Professor and Chairman of the Department on a full-time basis. He held this appointment until 1979, at which time he was made Emeritus Professor and Chairman. First and foremost he recruited a full-time academic staff, established an approved resident training program, and literally reshaped the Department.

In 1946 Dr DeWeese was asked to serve on the board of directors of the Portland Hearing Society, now known as the Portland Center for Hearing and Speech. He was instrumental in the establishment of the Kresge Research Institute of the West, one of the leading centers in the nation for the study of the hard-of-hearing and the deaf.

Dr DeWeese coauthored the *Textbook of Otolaryngology*, now in its seventh edition. Another book he authored is called *Dizziness — An Evaluation and Classification*, published in 1954. He also wrote over 30 papers that were published in various otolaryngologic and other scientific journals.

He was a member of many local and national societies; some of these include the Oregon State Medical Association, the American Medical Association, the American Academy of Ophthalmology and Otolaryngology, the American Laryngological, Rhinological and Otological Society, Inc, the American Laryngological Association, and the American Broncho-Esophagological Association. In 1959 he received the Award of Merit from the American Academy of Ophthalmology and Otolaryngology. He was elected to the offices of Director, Vice-president, and President of the American Board of Otolaryngology.

Dr DeWeese will be remembered especially for his ability to work with local civilian groups. This resulted in the establishment of the Kresge Hearing Research Institute. Most noteworthy is the fact that Dr DeWeese successfully entrusted the civilian community with the financial support of the Institute. This support is unique and accounts for a great deal of the Institute's success.

Dr DeWeese's first wife, Dorothy, predeceased him. He is survived by his wife, Edna, three daughters and one son, six grandchildren, and one great-grandchild.

Walter P. Work, MD

LETTERS TO THE EDITOR

To the Editor:

We read with interest the paper by Duncavage et al (Laryngotracheal Reconstruction With Composite Nasal Septal Cartilage Grafts, *Ann Otol Rhinol Laryngol* 1989;98:581-5) describing laryngotracheal reconstruction with composite nasal septal cartilage grafts. Our department has 15 years of experience in the reconstruction of the larynx by "composite nasal septal graft" after partial laryngectomy for carcinoma of the larynx.

The surgical treatment of T1b and T2 vocal cord carcinoma has been a subject of controversy for a long time. Despite the quantitative difference, patients with either small noninfiltrative glottic tumors or large invasive T1, T1b, or T2 glottic cancer remain in the same TNM category and receive neither qualitative oncologic distinction nor different therapeutic management. Radiotherapists and many laryngologists usually advocate primary irradiation, whereas others recommend partial laryngectomy.

The dilemma facing the laryngologist is whether these subgroups belong to the same oncologic category and deserve the same treatment, or whether they are different and thus have to be differently treated. We propose to call the subgroups of large invasive T1, T1b, or T2 glottic cancer "aggravated" T1, T1b, or T2 tumors (T1Ag, T1bAg, or T2Ag) and thus differentiate them by diagnosis and by treatment.

Traditionally, primary irradiation has been the optimal management for these cancers, with disease control rates approaching 80%. In our experience, patients with "aggravated" T1, T1b, or T2 tumors should receive partial or extended vertical laryngectomies as the procedures of choice. It is our policy to treat most horseshoe glottic lesions by frontal or frontolateral laryngectomy with immediate nasal mucoseptal reconstruction, as described in previous articles.[1,2]

Throughout the last 15 years, 26 glottic carcinoma patients underwent frontal or extended frontolateral laryngectomy in our department, with immediate reconstruction. Twenty-four patients were decannulated 5 to 10 days after the operation. The "neolarynx" thus obtained produced a good voice, and obviated the need for a permanent tracheostomy.

We have never determined the position of the graft to allow for ciliary flow from inferior to superior as Duncavage et al recommend. The trimming and adapting of the composite graft in the laryngeal gap is of essential importance. Wedging the graft in reverse position with a resulting — theoretic — localized reversed ciliary flow did not seem to be a significant factor. In our experience the nasoseptal graft should not be recommended in subglottic stenosis, because this graft cannot stand the high pressure of the cricoid ring and will atrophy. The hyoid muscle graft is in this case recommended.

In the paper by Duncavage et al, it is stated that "This report also documents for the first time cartilage preservation in a previously reconstructed laryngectomy patient." I wish to bring to the attention of these authors that in 1983 we published the microscopic findings in a patient after total laryngectomy, 4 years after we reconstructed his larynx with a nasal septal autograft.[3,4] Our histopathologic findings revealed that the laryngeal mucosa in the grafted area was of respiratory type, identical to the mucosa of the neighboring area. Cylindric ciliated cells were noted. The grafted cartilage was found to be vital and well preserved, with areas rich in nucleated chondrocytes and blood vessels. Little hyaline connective tissue was observed, and nucleated chondrocytes and blood vessels were found on both sides of the junction line between the remnants of thyroid cartilage and the nasal septal graft. Our work supported the study of Furstoss and Toohill[5] from 1973, who also found a well-preserved cartilage covered by respiratory mucosa in the septal graft used for experimental tracheal repair in dogs.

In 1985 we published a radiographic computed tomography study of the grafted larynx[6] that revealed that the grafted region in most of the patients has a cartilage density. This supports our histologic findings about the viability of the cartilage lined by a functional respiratory mucosa. The rigidity of the composite graft, the respiratory mucosal lining, and the vitality of the cartilage promote it as a good and compatible material for laryngeal and tracheal reconstruction.

We were surprised to read that the authors did not mention any of our many reports on the nasoseptal-grafted larynx published in the American literature since 1981, and I hope this new information will be of assistance to them.

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To the Editor:

The intent of our paper "Laryngotracheal Reconstruction With Composite Nasal Septal Cartilage Grafts" was to emphasize the use of the composite nasal septal graft for stenosis of the airway. We failed to emphasize that Laurian et al[1,2] were pioneers in using the composite nasal septal graft for reconstruction following partial laryngectomy.

I believe the matter of mucociliary flow is important. Toohill et al[3] reported preservation of respiratory epithelium on the composite nasal septal grafts in the subglottic area. They noted a change of the pseudostratified columnar epithelium to stratified squamous epithelium at the glottic level. I believe it is reasonable to orient the nasal septal cartilage graft to allow for ciliary flow when correcting subglottic or upper tracheal stenosis. It may not be necessary when reconstructing a partial laryngectomy defect, since the laryngeal epithelium is predominately squamous epithelium.[4]

I thank Drs Zohar and Talmi for bringing to my attention the placement of the composite nasal septal cartilage graft between the cut edges of the anterior cricoid cartilage. The posterior lamina of the cricoid cartilage almost always needs to be incised through to the underlying perichondrium. If this is not done, then it is very difficult in many situations of subglottic stenosis to make the graft stay in position.

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To the Editor:

In the early 1930s Paget[1] and Russell[2] described excessive nasality or hypernasality as twang quality that is made in the nose. Although there have been tremendous advances in the definition and description of hypernasality, Yanagisawa, Kmucha, and Estill (Role of the Soft Palate in Laryngeal Functions and Selected Voice Qualities. Simultaneous Velolaryngeal Videoendoscopy, *Ann Otol Rhinol Laryngol* 1990;99:18-28) used these 60-year-old descriptions of nasality. It is unfortunate that current definitions were overlooked.[3-7]

Yanagisawa and associates also said, "The percept of cleft palate speech is one of dullness" (p 26). According to Emerick and Hatten,[8] there is no such thing as "cleft palate speech"; rather, cleft palate is an etiologic category, not a symptomatic denotation. Landis and Fleming[9(p728)] believe the term cleft palate speech is vague and frequently used inappropriately to describe the voice problems that can result from velopharyngeal incompetence. Moll[10] also feels that the term "cleft palate speech" is essentially meaningless in describing the speech characteristics of individuals with cleft palate. Moll further states (Spriestersbach et al[11]) that "cleft palate speech" is not descriptive of the various speech dimensions that are affected, and that cleft palate individuals are quite heterogeneous in speech, ranging from normal to completely unintelligible.

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To the Editor:

Thank you very much for giving us the opportunity to respond to Dr Pannbacker's letter. This response was prepared by Jo Estill, one of our principal authors.

In the more recent references cited and suggested by Dr Pannbacker, the confusion between twang quality and nasality persists as it has in much of the speech literature that preceded it. For us, it was most satisfying to trace and develop a clearer understanding of "twang" quality from the observations made over the last 150 years from selected sources, beginning with Garcia[1] and Helmholtz[2] (in the mid-19th century), through Paget,[3] Russell,[4] and Bartholomew[5] (in the 1930s), through Lichte[6] and others (in the 1940s), to Van den Berg and Vennard[7] (1950s), to Sundberg[8] (1970s), and to Colton and Estill,[9] Laver,[10] and Titze[11] (1980s).

Our paper in the *Annals*[12] was an attempt to clarify the difference between nasal and "twang" qualities. "Twang" quality (like the concept of the term "register") suffers from being defined in two domains: perception and physiology. *Perceptually*, "twang" quality is identified as "nasal" or "hypernasal," implying that *physiologically* it is made in the nose as a consequence of an excessively open velopharyngeal port. *Acoustically*, an excessively open velopharyngeal port delivers a spectrum with few upper partials of any magnitude. Most of the energy is in the lower partials, leading to the percept of "dullness." On the other hand, a tightening of the aryepiglottic sphincter delivers a spectrum high in energy between 1.5 and 4 kHz, leading to the percept of "brightness"[6,10] such as that seen in the acoustic analysis of twang.[12,13]

The value of our own paper[13] is that simultaneous dual velolaryngeal endoscopy (SDVE) clarifies visually the differences between a totally nasal tone, a nasalized vowel, a nasalized twang, an oral twang, and the presence of twang as a valuable component of an acceptable operatic quality. The acoustic analysis confirms and reinforces the visual image.

The technique of SDVE coupled with acoustic analysis may help lift twang quality out of the nose and into the vocal tract where it belongs, as suggested as long ago as 1930 by Paget, who experimented with a rubber tube resonator shaped to produce the vowel /a/ and found that "if the tube was further pinched immediately in front of the opening of the reed tube, a definitely nasal twang was given to the vowel sound. This confirmed one of the author's personal observations *that the typical American twang is not due to nasal resonance but to a constriction of the pharynx.*"

The criticism of our use of the term "cleft palate speech" is well taken. It was an inappropriate allusion to the quality most frequently associated with the cleft palate population, probably because the quality of excessive nasality is often found in those with velopharyngeal incompetence. We shall be more careful in future papers.

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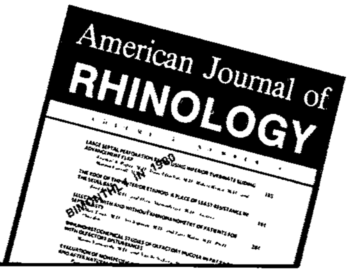

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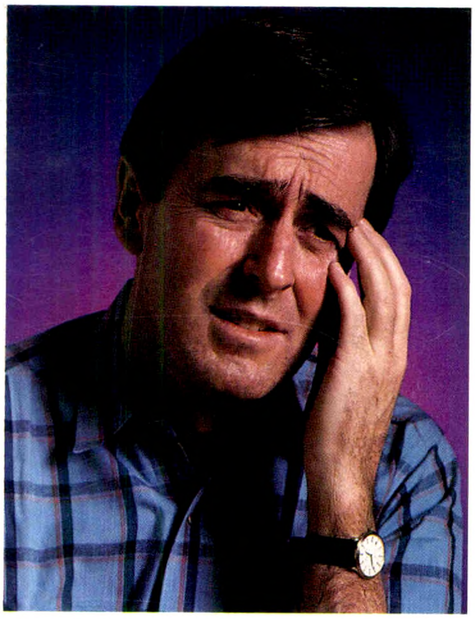

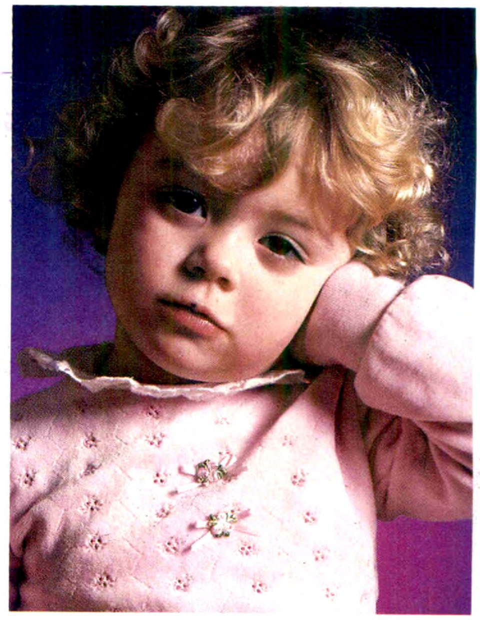

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- Stevens-Johnson syndrome, toxic epidermal necrolysis, and anaphylaxis have been reported rarely. Anaphylaxis may be more common in patients with a history of penicillin allergy.
- Gastrointestinal (mostly diarrhea): 2.5%.
- Symptoms of pseudomembranous colitis may appear either during or after antibiotic treatment.
- As with some penicillins and some other cephalosporins, transient hepatitis and cholestatic jaundice have been reported rarely.
- Rarely, reversible hyperactivity, nervousness, insomnia, confusion, hypertonia, dizziness, and somnolence have been reported.
- Other: eosinophilia, 2%; genital pruritus or vaginitis, less than 1% and, rarely, thrombocytopenia and reversible interstitial nephritis.

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- Slight elevations in hepatic enzymes.
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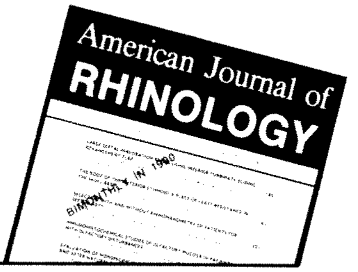

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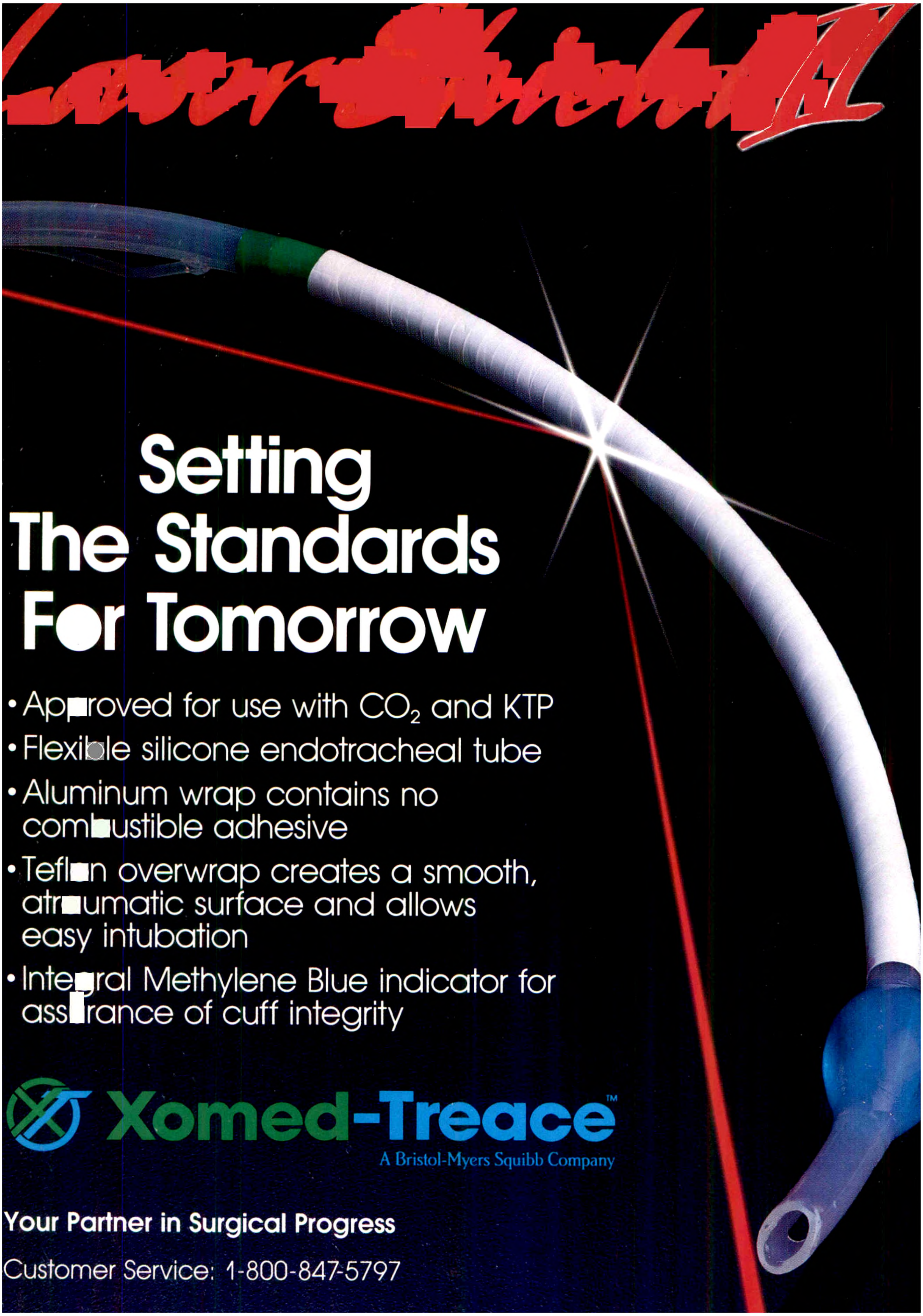

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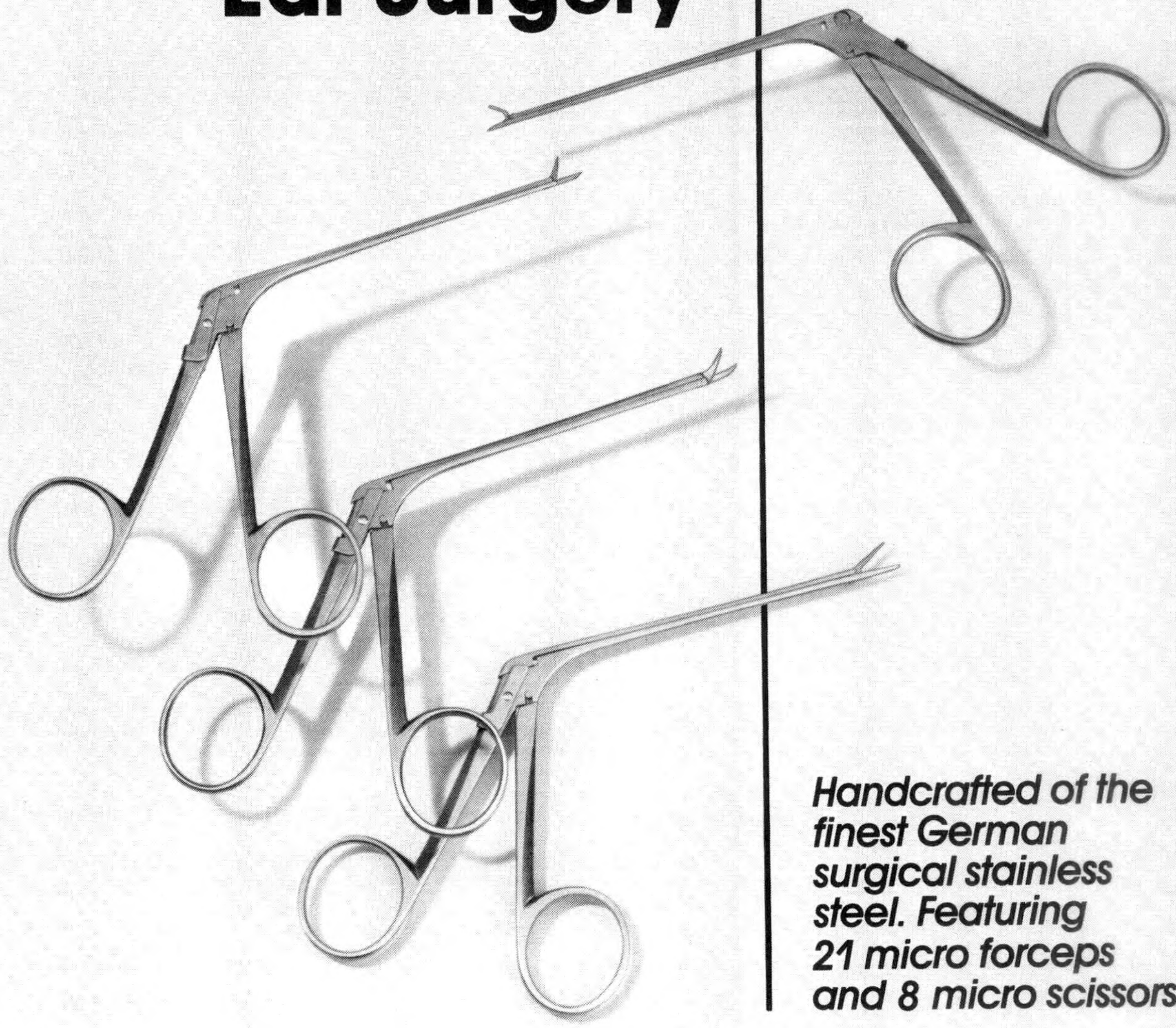

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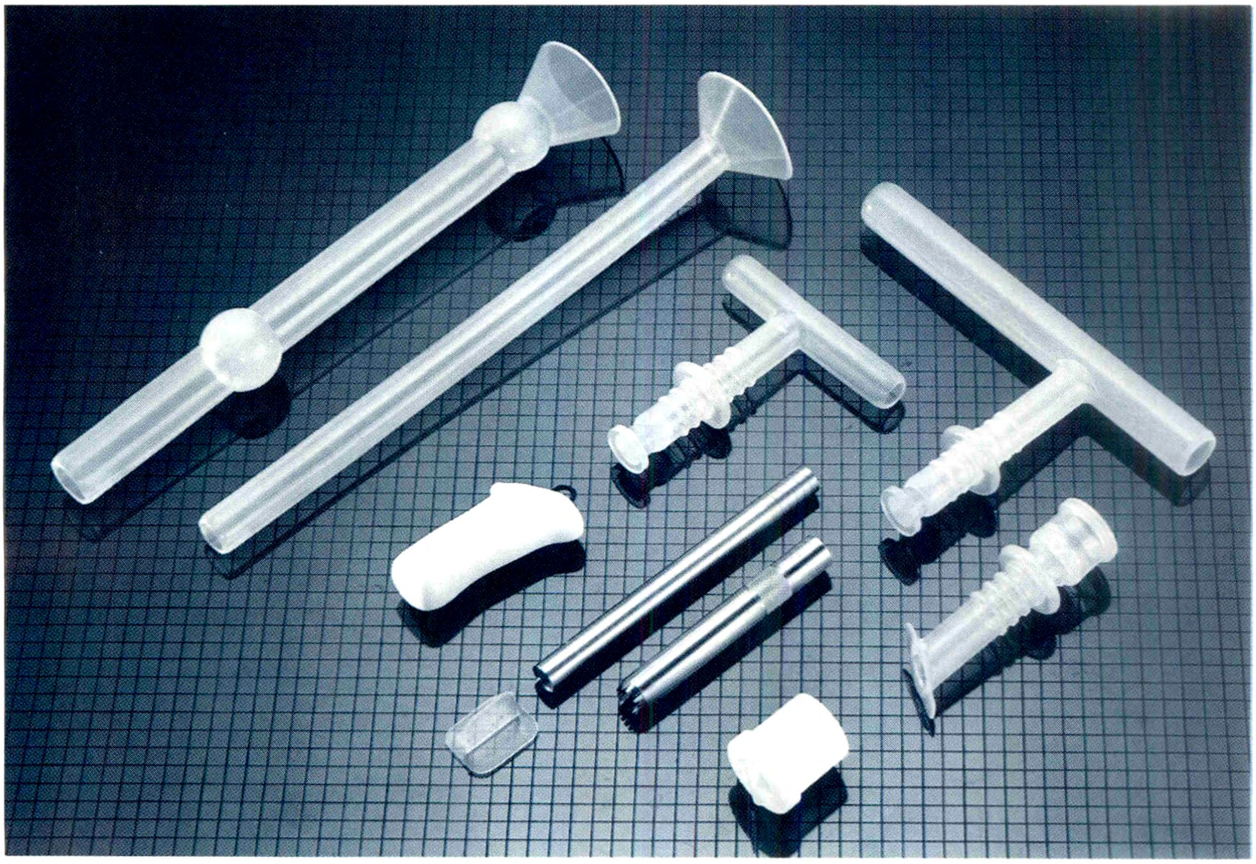

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ANNALS OF OTOLOGY, RHINOLOGY & LARYNGOLOGY (ISSN 0003-4894) is published monthly by Annals Publishing Company, 4507 Laclede Avenue, St Louis, MO 63108. Second-class postage paid at St Louis, Mo. POSTMASTER: Send address changes to Annals Publishing Company, 4507 Laclede Avenue, St Louis, MO 63108.

Printed on acid-free paper

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Ann Otol Rhinol Laryngol 99:1990

REMOVAL OF BLUNT FOREIGN BODIES FROM THE ESOPHAGUS

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Historically, removal of blunt foreign bodies from the esophagus by esophagoscopy under general anesthesia has been considered to be relatively safe and effective. In recent years, alternative techniques of blind removal with balloon catheters or bougies have been advocated. This paper reports 246 esophagoscopies performed over a 19-year period to remove blunt esophageal foreign bodies. Eighty-one percent of the foreign bodies were coins and 74% were in children under 3 years of age. There were no deaths, no perforations, and no instances of mediastinitis. The only complications encountered were those due to esophageal erosion and/or respiratory problems secondary to longstanding foreign bodies. In the author's opinion, esophagoscopy is the best method for removal of all esophageal foreign bodies. There simply does not seem to be a need for alternative methods involving blind removal.

KEY WORDS — bougienage, esophageal foreign bodies, esophagoscopy, Foley catheter, foreign body removal.

INTRODUCTION

Blunt objects are relatively common esophageal foreign bodies in children. Historically, their removal by esophagoscopy under general endotracheal anesthesia has been considered to be a relatively safe and effective procedure, especially with coin foreign bodies. In recent years, alternative techniques for removal of blunt foreign bodies have been increasingly advocated. The most popular alternative technique is removal with a Foley catheter under fluoroscopy.[1-9] Another method, pushing the foreign body into the stomach with a bougie, has also been advocated.[10,11] Foley catheter advocates often compare their technique to foreign body removal by esophagoscopy by quoting the complication rates for esophagoscopy removal of all types of foreign bodies,[12] and even esophagoscopy for indications other than foreign bodies.[13]

To give a fairer assessment of the complication rate for removal of only blunt foreign bodies by esophagoscopy, I am reporting our experiences with this technique in pediatric patients at the Los Angeles County-University of Southern California Medical Center over a 19-year period.

MATERIALS AND METHODS

Between January 1, 1971, and March 1, 1990, 246 esophagoscopies were performed to remove blunt foreign bodies from the esophagus of 231 pediatric patients. The number of procedures is greater than the number of patients because several patients with esophageal strictures, of which there were 21 in this series, required esophagoscopy on more than one occasion to remove different foreign bodies. For purposes of this paper, blunt foreign bodies are defined as those that do not have sharp edges or projections that could easily cut or perforate the esophagus. The medical records from the earlier years of this review were not always complete in all aspects. They were complete, however, regarding the presence or absence of complications.

Coins were by far the most common foreign bodies. One hundred ninety-six (80%) of the esophagoscopies were to remove coins. For this reason, the patients with coins will be described separately and in more detail than those with other foreign bodies.

Coin Foreign Bodies. Seventy-four percent of the 196 patients with coins in the esophagus were under 3 years of age and 25% were under 1 year of age. The youngest was 2 months old and the oldest was 16 years. Sixty percent were boys and 40% were girls.

The most common location of the coin was in the cervical esophagus just below the cricopharyngeus muscle. It was found in this location in 95% of the patients. In 5%, the coin was located in the thoracic esophagus at the level of esophageal compression by the aortic arch and left main stem bronchus, or at a stricture.

The records of 157 patients contained information regarding the duration of time that the coins were in the esophagus. Eighty-six (55%) of these patients were seen within 24 hours of having swallowed the coin. Twenty-one were seen between 24 and 48 hours after ingestion, 26 were seen after 3 days, and 24 were not seen until 7 days to over 2 months after ingestion. The most common presenting complaint was that of having swallowed a coin. This was the case with all of the patients seen within 2 or 3 days of the ingestion. Those with foreign bodies of longer duration often had no definite history of ingestion but had one or more of the following complaints: dysphagia and vomiting, a cough that

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Presented at the meeting of the American Broncho-Esophagological Association, Palm Beach, Florida, May 2-3, 1990.

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was aggravated by eating, noisy breathing, and fever. The coins in these cases were incidental findings on chest radiographs taken as part of the evaluation of the above symptoms. The presence of coin foreign bodies was confirmed by chest radiographs in all patients.

Although some of our records were incomplete, we estimate that 50% or more of the patients with coins lodged in the esophagus for longer than 3 days, and every patient with coins longer than 7 days, presented with some type of respiratory symptoms. Several were febrile and were diagnosed as having respiratory infections. Nine had radiographic evidence of pneumonitis, presumably secondary to aspiration.

Once the foreign bodies were diagnosed, esophagoscopies were usually performed within 24 hours. All patients underwent esophagoscopy in the operating room under general endotracheal anesthesia with intravenous succinylcholine chloride muscle paralysis. The Jesberg rigid pediatric, adolescent, or short adult esophagoscopes were used in all cases. The actual time of the esophagoscopy varied from 4 to 13 minutes in the uncomplicated cases. In several patients with marked esophageal erosion and edema, including one in whom one of two coins had eroded through the anterior esophageal wall, the esophagoscopy took from 15 minutes to over 1 hour. The total time the patient was in the operating room usually was 15 to 20 minutes longer than the esophagoscopy time. The coins were exposed with the esophagoscope and were grasped with forceps under direct vision. The esophagoscope was then carefully removed with the coin trailing it. After removal of the coin the esophagoscope was reinserted and the site of foreign body lodgment was examined for mucosal erosions or for a possible second foreign body.

Foreign Bodies Other Than Coins. Fifty esophagoscopies were performed to remove blunt foreign bodies other than coins. The most common of these foreign bodies was meat, usually retained above a stricture, in 20 patients. Vegetable matter, nuts, and seeds were removed from 14 patients. Rounded metal, plastic, or glass objects and trinkets were also found in 14 patients, including one disc battery. One teenager swallowed a dental retainer and another ingested a toothbrush.

The age distribution was older than in the patients with coin foreign bodies, with 56% being over 3 years of age. Only 5 patients were under 1 year of age, and 11 (22%) were teenagers.

The duration and symptoms of these foreign bodies were similar to those of the patients with coins except that vomiting was a more prominent symptom with meat foreign bodies. Two patients, a 9-month-old with a metal shoe trinket and a 14-month-old with a metal button, whose foreign bodies had been in place for over 7 days, had fever and stridor preoperatively.

In those with opaque foreign bodies, the diagnosis was confirmed by chest radiograph. With nonopaque foreign bodies, barium esophagograms were often performed to aid in the diagnosis. In patients with known strictures who developed abrupt dysphagia and vomiting, however, esophagograms often were not done prior to esophagoscopy. As with coins, the foreign bodies were removed with direct vision through a Jesberg esophagoscope under general endotracheal anesthesia.

RESULTS

Coin Foreign Bodies. In 187 patients the coins were removed with the esophagoscope. In 9 patients, the coins were found to have passed into the stomach from the muscle relaxation induced by the general anesthesia; the coins passed through their gastrointestinal tracts without complications. A total of 206 coins were removed from the 196 patients. The type of coin was stated in 192 instances. These included 127 pennies, 30 quarters, 21 nickels, and 14 dimes. The majority of pennies, nickels, and dimes were in patients under 3 years of age. The majority of quarters were found in patients 3 years of age and older.

Esophageal injury secondary to the foreign body with erosion, edema, and sometimes granulation tissue was noted in 47 patients (24%). Mucosal erosions were found in 39% of the patients under 1 year of age and in 90% of patients with a coin present for more than 7 days. Twelve patients with a coin present no longer than 3 days had mucosal erosions. One patient, 1½ years old, with a history of noisy breathing for 6 months, had erosion through the anterior esophageal wall by one of two coins.

Multiple foreign bodies were found in 10 of the 196 patients. Eight patients had two coins; one had a coin and three pieces of meat; one had three coins, multiple wads of paper, string, and two pieces of plastic. The time since suspected foreign body ingestion was noted in 8 of these 10 patients and was 24 hours or less in 5 of the 8.

There were no deaths, no perforations, no instances of mediastinitis, and actually no complications secondary to insertion of the esophagoscope and removal of the coins. Fourteen patients had respiratory complications either from long-standing foreign bodies or from preexisting pulmonary disease, exacerbated by the endotracheal anesthesia. Eight of these 14, 2 of whom had periesophageal inflammation, had a croupy cough and mild stridor postoperatively. All 8 were under 2 years of age; 7 of the 8 had a preoperative diagnosis of a respiratory illness; and the coin had been in the esophagus longer than 7 days in 5 of the 8. The other 6 of the

14 were not croupy, but had postoperative flare-ups of their preexisting lung disease.

In addition to the 14 patients described above, 3 other patients had adverse incidents from the endotracheal anesthesia. One 3-year-old patient was accidentally extubated during the procedure. She developed laryngospasm that was relieved by intravenous succinylcholine and ventilation by face mask. The patient recovered without any ill effects from this incident. A second patient developed laryngospasm after extubation at the end of the procedure, requiring reintubation. This patient also recovered without complications. A third patient vomited while recovering from the anesthesia with the endotracheal tube still in place, and vomitus was suctioned from the endotracheal tube. Because of this, the patient was kept in the hospital 24 hours postoperatively for observation, but he developed no pulmonary problems. None of these 3 patients actually suffered any adverse effects from the incidents described above.

Overall, 80% of the patients left the hospital within 24 hours after the esophagoscopy, and 94% left within 48 hours. Eleven patients were hospitalized longer than 48 hours; the longest period was 6 days. Until the middle 1980s, the standard of care at the Medical Center was to keep patients hospitalized overnight after endoscopic procedures. With the present cost-conscious emphasis on day procedures and early discharge, many would have been discharged in a shorter time. Since our earlier report,[14] 63% of the patients have been discharged within 12 hours after their esophagoscopy, and many of these were discharged far earlier than 12 hours.

Foreign Bodies Other Than Coins. There were no deaths, no perforations, and no instances of mediastinitis. All but one of the patients were discharged within 24 hours after the esophagoscopy, and many in recent years were discharged after only a few hours. The 9-month-old mentioned earlier who had ingested a metal shoe trinket had a fever of 40°C preoperatively secondary to an abscess formed by erosion of the posterior esophageal wall just below the cricopharyngeus. She also had chest radiographic evidence of pneumonitis and had stridor preoperatively. She suffered no complications from the esophagoscopy, but her foreign body complications necessitated 19 days' postoperative hospitalization for intravenous antibiotic treatment.

DISCUSSION

Since 1966, when Bigler[15] reported removal of a jack and a coin from the esophagus with Foley catheters in 6- and 11-year-old patients, respectively, an increasing number of papers have been published regarding this alternative to removal by esophagoscopy.[1-9,16-18] Even a third technique, pushing the foreign body into the stomach with a bougie, has recently been advocated.[10,11] As McGuirt[19] stated, those advocating the alternative methods generally are physicians who were not specifically trained in foreign body endoscopy. Those who are trained in foreign body endoscopy usually favor esophagoscopy as the preferred method for removal of all esophageal foreign bodies. While each of these methods appear to be successful more often than not, it is worth deciding by fair comparison which should be the method of choice.

Those advocating balloon catheter or bougienage techniques cite the following advantages over esophagoscopy: 1) avoidance of the use of an operating suite, 2) avoidance of hospitalization, 3) avoidance of the risks of general anesthesia and endotracheal intubation, and 4) avoidance of the risks of esophagoscopy. At a glance, these may seem to be worthwhile arguments, but on closer examination their foundation is not strong. For instance, the alternative methods are recommended only for blunt foreign bodies, usually coins, of short duration without preexisting esophageal disease or other factors that make complications more likely. These are precisely the foreign bodies that are the easiest and safest to remove by esophagoscopy. Any foreign body that can be removed by a Foley catheter or a bougie can be removed just as easily and perhaps more safely under direct vision with esophagoscopy. Foreign bodies with any suggestion of complications are not considered candidates for the alternative blind methods of extraction.[4,5,11] These are acknowledged to be more safely managed by esophagoscopy. It seems logical that the safest technique for removal of complicated foreign bodies should also be the safest technique for removal of uncomplicated foreign bodies.

Even though the Foley catheter technique is used only for uncomplicated foreign bodies, its advocates cite the complication rate of esophagoscopy for all reasons and for removal of all foreign bodies — sharp as well as blunt, complicated as well as uncomplicated — as evidence to support their method. In the past, there were no papers reporting a series of patients undergoing esophagoscopy to remove only blunt foreign bodies. Generally reported was removal of all foreign bodies, including sharp and penetrating ones. Reported complications were secondary to the foreign bodies, not the esophagoscopies. For instance, in a series of 2,394 esophagoscopies for foreign bodies in patients of all ages, there were only 25 perforations, and these were caused by the foreign bodies.[20] One hundred thirty-four children in that same series had coins removed by esophagoscopy without complications.

Our results — no deaths or perforations in 246 esophagoscopies to remove blunt foreign bodies — testify to the relative safety of this procedure in the hands of skilled endoscopists and skilled anesthesiologists. This technique is humane and controlled, and especially with foreign bodies of short duration, is probably one of the safest operations known to modern medicine. From the standpoint of patient safety, there simply does not seem to be a need for alternative techniques involving blind removal. All of the problems encountered with our patients were either related to endotracheal intubation or were exacerbations of preexisting respiratory illnesses. The alternative methods do avoid the use of general endotracheal anesthesia with its slight risk. On the other hand, patients with preexisting respiratory illnesses might be made worse by the struggling and vomiting that accompany extraction of foreign bodies by the blind techniques.

McGuirt's[19] survey of multiple specialties in 1982 revealed 19 nosebleeds, 4 instances of coins lodged in the nose, 1 episode of hyperpyrexia, and 1 instance of laryngospasm with the Foley catheter method. Although it was not detected in the survey, a death from airway obstruction was mentioned in the discussion following McGuirt's presentation.[21] A more recent survey of pediatric radiologists by Campbell and Condon[7] reported an extraordinary number of Foley catheter procedures, over 2,500, with "only one potentially serious but reversible complication." This survey also reported a high incidence of complications from esophagoscopic removal of blunt foreign bodies, including 31 esophageal perforations, 6 cases of mediastinitis, and 3 deaths. That was based on hearsay data supplied by pediatric radiologists. Our experience as reported in this paper, as well as the above discussion, casts doubt upon the accuracy of both sets of data reported by Campbell and Condon.[7]

Eighteen respondents in the latter survey[7] mentioned hearing of a death "in the Boston area" with the Foley catheter technique, but the authors were unable to confirm it. They were unable because the death did not occur in Boston, as was assumed because it was mentioned by Gerald Healy, MD, of Boston, at an American Academy of Pediatrics meeting. This unfortunate complication was witnessed by Dr Healy, but it was when he was in the armed services and before he came to Boston Children's Hospital (G. B. Healy, personal communication, March 1990). Upon attempted removal of a quarter from the esophagus with a Foley catheter by a radiologist and a pediatrician, the coin was flipped into the larynx, and it became impacted in the ventricles, obstructing the airway. Dr Healy was called emergently but too late to save the child. For personal reasons, the physicians involved have never reported this occurrence. It is human nature for a physician having such a tragic complication to be reluctant to discuss it or to publicize it. This reluctance leads to the disturbing thought that as was stated in a 1982 edition of *Medical World News*,[22] we do not know the true incidence of these problems.

Campbell and Condon[7] say that airway obstruction is unlikely with the Foley catheter method because "even the smallest coin" is too large to enter the subglottic airway of young children. The tragic case described above shows that the coin does not have to enter the subglottic space to produce fatal airway obstruction. It also shows the need not only to have resuscitative and airway equipment immediately available, but also to have someone there who is skilled in the use of that equipment in emergency situations. That requirement is mentioned in two papers that favor the Foley catheter method.[4,5] However, unless someone trained and experienced in removing airway foreign bodies is present, that requirement is not adequately fulfilled.

Another stated requirement for Foley catheter removal of foreign bodies is a "cooperative patient."[4,5,19] This would seem to rule out at least any child under 3 years of age, which included 74% of our patients with coins in the esophagus.

Some recent statements made to justify the alternative techniques verge on the ludicrous. Responding to letters to the editor from Crysdale[23] and Kibblewhite and Riding[24] that referred to the Foley catheter method as barbaric, Rubin[25] states that a compassionate radiologist using a Foley catheter is no more anxiety-provoking than an anesthesiologist inducing anesthesia or an otolaryngologist removing wax from the ear. Campbell and Condon[7] say that Foley catheter extraction by an inexperienced radiologist is no more hazardous than pediatric anesthesia by someone inexperienced in it or pediatric endoscopy by an individual with no training or experience. These statements may be true, but none of the three cited examples should be involved in the elective removal of esophageal foreign bodies.

Another advantage of direct examination by esophagoscopy is in evaluating the degree of esophageal injury inflicted by the foreign body and in searching for multiple foreign bodies.[26] Ten patients in our series with a history and/or radiographic evidence of a coin foreign body had multiple foreign bodies. Three had unsuspected radiolucent foreign bodies in addition to the coin. One patient with two coins had a definite history only of ingesting one coin approximately 12 hours prior to esophagoscopy. The chest radiograph showed only one coin in the cervical esophagus. This patient as well as those with radiolucent foreign bodies, if managed by the Foley catheter technique, would have been at risk for having one of the foreign bodies left in the pharynx, from which it would likely pass back into the esophagus or into the larynx.

Not all radiologists favor the Foley catheter technique. An editorial by Berdon, editor of the journal *Pediatric Radiology*, referred to it as a step back-ward in pediatrics.[27] Tenenbein,[28] a pediatric emergency medicine specialist, said of the Foley catheter method, "I tried it a few times and although successful I was quite distressed over the toll this procedure exacted of my patients."

Regarding cost-effectiveness, perhaps the Foley catheter and bougienage methods do have an advantage in being simpler and avoiding the use of an operating room and general anesthesia. On the other hand, almost all patients with uncomplicated foreign bodies can be discharged within only a few hours after esophagoscopy. At many institutions, these can be done as in-and-out day procedures. At our large county-university medical center, because of its huge load of emergency trauma patients, some of our patients with foreign bodies of the esophagus undergo longer delays in getting to the operating room than would be the case at less crowded institutions. Sometimes the esophagoscopies are not done until late at night and then the patients are not discharged until the next day, whereas they could have been discharged in a few hours if seen at a more convenient time. Even so, the majority of our patients in recent years have been discharged within 12 hours after the procedure.

This author agrees with Campbell and Condon[7] when they say that any method of intervention in medical practice carries some degree of intrinsic risk to the patient. That risk exists for general anesthesia for any procedure; it exists for esophagoscopy; it also exists for the alternative techniques of foreign body removal using balloon catheters or bougies. On the other hand, preservation of the airway is acknowledged to be the most important consideration in foreign body management.[2,4,5,29] It is best accomplished by general endotracheal anesthesia and foreign body removal under direct vision by esophagoscopy.

ADDENDUM

REPORT OF FOREIGN BODY SURVEY

Because this author doubts the accuracy of both sets of figures in the survey by Campbell and Condon,[7] a survey was conducted of the active members of the American Broncho-Esophagological Association and the American Society of Pediatric Otolaryngology. Those who belong to both associations were polled only once. Approximately 230 questionnaires were mailed and 154 replies were received. The survey consisted of four questions.

1. *Have you ever had a perforation of the esophagus as a complication of esophagoscopic removal of an uncomplicated coin foreign body?* All 154 respondents answered no.

2. *Do you know of any perforations occurring from esophagoscopic removal of an uncomplicated coin foreign body? If yes, what was the specialty of the endoscopist?* There were 152 answers of no. The 2 yes answers indicated that the endoscopists were a pediatric surgeon and an otolaryngology resident, respectively.

3. *Have you had, or do you know of, a death of a patient as a complication of esophagoscopic removal of a coin foreign body? If yes, please describe the details.* There were 147 answers of no. There were 7 answers of yes. Aspiration of gastric contents was the cause in three patients, two of whom vomited while under anesthesia. A third patient aspirated through a traumatic tracheoesophageal fistula resulting from a long-standing foreign body at a stricture from a prior congenital tracheoesophageal fistula repair. This patient was mentioned by three physicians at the same hospital; hence, the seven replies accounted for only five deaths. One patient died of unrecognized meningitis in the recovery room after successful coin removal. One respondent simply said, "By thoracic surgeon in 1954-55" and gave no further details.

4. *Do you know of any complications that have occurred from Foley catheter removal of coins from the esophagus? If yes, what were the complications? Did these occur in your area or elsewhere?* There were 109 answers of no, and 45 answers of yes. Twenty-seven of the 45 "yes" respondents reported airway obstruction. Twenty-two reported these as having occurred elsewhere, while 5 reported them as occurring locally. It was difficult to determine how much overlap there was in those reporting episodes occurring elsewhere, but this survey definitely detected seven, and possibly more, separate patients who suffered airway obstruction from Foley catheter extraction of esophageal foreign bodies. Seventeen respondents mentioned a death. Twelve of the 17 mentioned Dr Healy or Boston, referring to the death witnessed by Healy, which, as stated above, actually did not happen in Boston. Five others only said "elsewhere." The author assumes that all 17 are referring to that one case reported by Healy. However, this assumption may be incorrect, and more than one death may have been reported. One respondent mentioned a survival with severe hypoxic injury.

In addition to the instances of obstruction, one episode of transient apnea was reported. One physician mentioned a case in which a coin was displaced from the esophagus to a main stem bronchus, but provided no further details. Seven instances of esophageal injury were reported. In three cases, actual perforation of the esophagus occurred, one of which was said to have required anterior and posterior mediastinotomy, massive doses of antibiotics, and 6 weeks of hospitalization. Four other cases of bleeding and/or concern regarding perforation were also reported. One reply reported an instance of a general surgeon's using a Foley catheter under general endotracheal anesthesia and missing a second coin. A second anesthetic was required for removal of the second coin. Two respondents reported foreign bodies lost in the nasopharynx and requiring otolaryngology consultation, at least one of which required general anesthesia for removal. One patient had aspiration pneumonia. Eight physicians reported that patients were sent to them after failure to remove coins with Foley catheters. One stated that the patient was "worked on for 45 minutes in radiology before transfer." One other physician said that he suspected complications have occurred in his area but could not confirm them. Several others said that they had heard of complications, but did not state what they were.

The author acknowledges that this survey is biased, as was that of Campbell and Condon,[7] because it is based on information obtained from endoscopists. Nevertheless, two impressions can be gained from this survey. One is that complications occur very rarely with esophagoscopic removal of uncomplicated coin foreign bodies by well-trained endoscopists. The other is that there is significantly more risk to the patient from the Foley catheter procedure than previous publications have indicated. It seems that these risks and the alternative of removal by esophagoscopy should be explained to the parents of a child undergoing the Foley catheter procedure according to the concept of informed consent.

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CARE OF THE PROFESSIONAL VOICE

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Ann Otol Rhinol Laryngol 99:1990

EFFECT OF BLEOMYCIN ON HEMATOPORPHYRIN DERIVATIVE PHOTOTHERAPY OF SOLID TUMORS

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Hematoporphyrin derivative phototherapy (HpD-PT) has been successfully used to localize and treat superficial squamous cell cancers. Bleomycin sulfate is a glycopeptide antibiotic that has antineoplastic properties against squamous cell cancers. Because both HpD-PT and bleomycin chemotherapy are accepted forms of treatment for squamous cell cancer and their cytotoxicity is mediated by singlet oxygen and oxygen radicals, we studied the possibility of enhancing the response of solid tumors to HpD-PT by combining this modality with systemic bleomycin chemotherapy in a murine tumor model. Bleomycin did not enhance HpD-PT significantly. Also, we are not confident that HpD-PT alone or in combination with other agents can eradicate solid tumors; it certainly did not in this syngeneic murine tumor model.

KEY WORDS — hematoporphyrin derivative phototherapy, laser therapy, photodynamic therapy, photoradiation therapy.

INTRODUCTION

Hematoporphyrin derivative (HpD) localizes preferentially in various animal and human tumors. Stimulation of this localized HpD with visible light in the presence of oxygen produces a photodynamic reaction that destroys the host cell. The exact mechanism of this cytotoxic action is unknown but is thought to be mediated by singlet oxygen and other toxic oxygen radicals generated during the photodynamic reaction.[1-5]

These properties allow the effective use of HpD phototherapy (HpD-PT) in the treatment of human tumors.[6-12] However, its efficacy for treatment of solid tumors is limited by the extent of penetration of the activating light.[13] This limitation determines the size of solid tumors that can be treated successfully with this form of therapy.

Attempts have been made to combine HpD-PT with other forms of therapy to enhance its cytotoxic and tumoricidal effects. Previous work in our laboratory has shown that in mice, simultaneous cooling of solid tumors with cryosurgical techniques leads to a significant enhancement of necrosis.[14] The combination of ionizing radiation with HpD-PT has had some success in a rat tumor-host model.[15] Glucocorticoids have been shown to enhance the effect of HpD-PT on lung carcinoma and melanoma in a mouse tumor-host model.[16] Specific antitumor monoclonal antibodies conjugated with HpD as an immunotoxin have exhibited significantly enhanced killing of tumor cells in vitro.[17] Edell and Cortese[18] have shown that the chemotherapeutic agent doxorubicin hydrochloride (Adriamycin) significantly increases the necrosis of Walker 256 carcinosarcoma achieved with HpD-PT in Sprague-Dawley rats. Cowled et al[19] found increased tumor control in vitro by combinations of HpD-PT with doxorubicin and methotrexate but not with cyclophosphamide, thiotepa, vincristine sulfate, or 5-fluorouracil.[19]

Bleomycin sulfate is an antineoplastic agent known to be effective in the treatment of squamous cell carcinomas of the head and neck.[20] Its mechanism of action involves the generation of toxic oxygen radicals and subsequent cytotoxicity, similar to that of the photodynamic reaction involved in HpD-PT.[21-24]

In an attempt to find a means by which the tumoricidal effect of HpD-PT could be increased in solid tumors, we studied the effect of systemic bleomycin therapy on the tumor necrosis induced by HpD-PT in a syngeneic murine tumor-host model.

METHODS

The light delivery system, HpD, tumor model, and calculation of treatment-induced tumor necrosis used in this study were identical to those in our previous work.[14]

Light Delivery System. An 18-W argon ion laser (Spectra-Physics, model 171) was used to pump a continuous-wave Spectra-Physics (model 375) dye laser (rhodamine B). The laser produced light at 630 nm by using a dichroic tuning filter. The output of the laser was coupled to the proximal end of a

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Presented at the meeting of the American Broncho-Esophagological Association, San Francisco, California, April 1-2, 1989.

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RADIUS OF NECROSIS

Group	*N*	*Radius (mm; mean ± SD)*
Experimental		
HpD, light, bleomycin	50	1.65±0.35
HpD, light	50	1.55±0.31
Control		
HpD, bleomycin	52	0.98±0.40
HpD	47	1.13±0.41
Bleomycin	45	1.19±0.43
Light, bleomycin	50	1.31±0.36
Light	46	1.41±0.41
No treatment	41	1.16±0.36

HpD — hematoporphyrin derivative.

quartz optical fiber 1 m long and 400 μm in diameter (Quartz et Silice, Paris, France). The wavelength of the light was determined with a calibrated double-grating monochromator (Instruments SA, model H.20V). The dichroic filter was rotated by its micrometer screw while the laser output on a diffuse surface was viewed through the monochromator until the desired spectral line was observed. Power exiting from the distal tip of the optical fiber was measured with a calibrated power meter (Spectra-Physics, model 404) that had a flat response between 400 and 900 nm. A power level of 100 mW was used.

Tumor Model. This model is a typical virus-induced mammary tumor transplanted into adult female C3H/HeN syngeneic mice. The tumor line was maintained by serial transplantation of 10^6 cells in single-cell suspensions. The recipient site was in the left flank in all the mice. The tumor mass doubling time was 7 to 10 days, and untreated mice died, at 8 to 12 weeks after transplantation of tumor, as a consequence of metastasis.

Hematoporphyrin Derivative. The HpD used in this experiment was produced originally according to Lipson et al[25] and as described in detail by Carpenter et al[26] and Cortese and Kinsey.[9] It is an incompletely characterized mixture of components resulting from the acetylation and hydrolysis of commercial hematoporphyrin.

Bleomycin. Commercially available, sterile bleomycin sulfate (Blenoxane, Bristol-Myers Oncology) was used at a dose of 0.01 U/g of body weight, based on LD10 for mice of <15 U/kg intraperitoneally daily for 5 days.

Treatment. When the tumors reached a mean (±SD) radius of 1.0±0.2 cm, the mice were randomly assigned to eight groups (41 to 50 mice per group). The mice that were given HpD received a dose of 0.025 mg/g body weight injected intraperitoneally 24 hours before the interstitial light treatment. After receiving HpD they were protected from incidental light exposure. The bleomycin was given intraperitoneally every day for 3 days prior to HpD-PT and for 2 days afterward (total, 5 days). In the light-treated groups, a single fiberoptic probe was inserted through the skin and used to deliver light into the tumors at wavelength 630 nm and 100 mW for 15 minutes.

In previous studies,[14] intratumor temperatures were measured with a calibrated thermistor probe fitted into a hypodermic needle (Yellow Springs Instruments, series 524). The measurements were made 2.5 mm from the tumor surface and 2.0 to 2.5 mm from the optical fiber; the temperatures were 43°C to 55°C.

In sham experiments, mechanical insertion of fiberoptic probes into tumors without delivery of light or HpD is responsible for less than 1 mm of necrosis.[14,27]

Measurement of Tumor Necrosis. All mice were killed at 48 hours after phototherapy and 5 days of bleomycin administration, and the tumors were excised. After the tumors were fixed in formalin for 5 days, they were transected in a plane that had contained the distal tip of the optical fiber during interstitial light treatment. A section from the transected face of each tumor was fixed, mounted, and stained with hematoxylin and eosin. Black-and-white same-size photomicrographs were made of each slide on Kodak Panatomic-X film, and enlargements (x10) of these were printed on 20 x 25-cm sheets. The area of necrosis on the photographic enlargement was traced onto fine-grid cross-section tracing paper while the slide was examined simultaneously under the microscope to ensure accurate reproduction of the necrotic area from photograph to grid paper. The number of squares within the necrotic area was multiplied by the area of an individual square (6.452 mm^2) to give the area of necrosis on the photographic enlargement.

To determine the absolute cross-sectional area of necrosis on histologic slides, an area scale factor was calculated from a direct measurement of the same identifiable distance on both the slide and the photographic enlargement of each tumor specimen. From these measurements, a mean magnification ratio for all tumors provided the linear correction factor that, when squared, yielded the area scale factor. The cross-sectional area of necrosis within each tumor specimen on the histologic slides was then computed by multiplying the area of necrosis on the enlargement by the area scale factor. The radius of necrosis was determined by $r = (A/\pi)^{1/2}$ in which A is area.

RESULTS

The radii of necrosis for the two experimental and six control groups are shown in the Table. The largest mean radius of necrosis was induced in the group treated with HpD-PT and bleomycin, and the second largest was in the group treated only with HpD-PT. All groups were compared in a total of 28 two-sample *t* tests. The two experimental groups differ significantly ($p < .05$) from all control groups except that group treated with light only. No significant difference in mean radius of necrosis was observed between the two experimental groups ($p > .05$, two-sample *t* test).

DISCUSSION

The absence of a significant additive effect from these two modalities most likely is due to their different sites of action. It has been proposed that the site of action of HpD is the cell membrane.[14] Bleomycin must interact in the cell nuclei in the presence of DNA to achieve scission and subsequent damage.

Saunders and Alexander[28] have noted that decreased uptake at the cell membrane level can lead to increased cellular resistance to bleomycin. It is possible that HpD interferes with the uptake of bleomycin, thereby limiting its effectiveness and limiting any significant additive effect. On the other hand, the outcome with doxorubicin is improved, but the studies were conducted in different animal tumor models. In noting the significant enhancement of HpD-PT with doxorubicin, Cowled et al[19] and Edell and Cortese[18] postulated similar mechanisms and sites of action. Saunders and Alexander[28] postulated that doxorubicin may exert its main cytotoxic action at the cell surface.

The largest radii of necrosis achieved with bleomycin in our experiments occurred in a regimen that included treatment with light. Others[29,30] have suggested that the cytotoxicity of bleomycin is enhanced by hyperthermia, and our data tend to support this idea because treatment with light increases the tissue temperature.

Some of the chemotherapeutic agents used in clinical oncology enhance the effect of HpD-PT and show promise for future use in combination with HpD-PT to treat solid human tumors. Because bleomycin did not significantly enhance HpD-PT in our study, we are not confident that HpD-PT alone or in combination with other agents can eradicate solid tumors.

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INTERNATIONAL HEARING AID CONFERENCE: SIGNAL PROCESSING, FITTING, & EFFICACY

The International Hearing Aid Conference: Signal Processing, Fitting, & Efficacy will be held June 21-23, 1991, at The University of Iowa, Iowa City, Iowa. The organizing committee includes Richard S. Tyler, PhD (Signal Processing), Chaslav V. Pavlovic, PhD (Fitting), and Ruth A. Bentler, PhD (Efficacy). Further information may be obtained from any member of the organizing committee at the Department of Speech Pathology and Audiology, The University of Iowa, Iowa City, IA 52242; (319) 335-8726, FAX (319) 335-8851.

Ann Otol Rhinol Laryngol 99:1990

PLATYSMA MYOCUTANEOUS FLAP FOR REPAIR OF HYPOPHARYNGEAL STRICTURES

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Hypopharyngeal strictures, either isolated or in conjunction with laryngeal and esophageal strictures, can occur following lye ingestion. Extensive stricture formation requires reconstruction to create a functional funnel system that empties below the cricoid. Esophageal replacement is not a substitute for adequate hypopharyngeal reconstruction. The pectoralis major muscle is often inadequate, because it yields too much bulk and often leads to continued aspiration. The platysma myocutaneous flap for hyopharyngeal reconstruction has not been previously reported. The inferiorly based platysma myocutaneous flap was used in two of our patients with lye burns, and bilateral superiorly based flaps were used in one. All are able to eat normally and have no significant stenosis. The platysma myocutaneous flap is a relatively simple and reliable alternative that is within the capability of every head and neck surgeon.

KEY WORDS — hypopharyngeal strictures, lye ingestion, platysma myocutaneous flap.

Ingested caustics produce a spectrum of injury depending on their form, concentration, and chemical nature. Solid, crystalline caustics tend to adhere to mucosa and cause proximal burns, while liquids, because of easy deglutition, cause more diffuse damage to the esophagus and stomach. The extent of hypopharyngeal and esophageal burns does not necessarily correlate with that of oral burns. Endoscopy is considered to be the standard for evaluating esophageal injury. The upper gastrointestinal tract can be adequately examined with the use of a flexible scope, and a smaller-caliber pediatric endoscope may be useful in the presence of stricture. However, supplemental rigid tube inspection of the hypopharynx is vital, as this area is poorly viewed with the flexible system.

Hypopharyngeal stenosis is an infrequent but ominous complication following caustic ingestion (Fig 1). Extensive scarring and hypopharyngeal stenosis results in dysphagia and aspiration. Conservative treatment by repeat bougienage and endoscopic or laser lysis of scar tissue is usually inadequate, as the stenosis rapidly redevelops. The diversity of techniques available for reconstruction attests to the lack of a solution to the problem.

Techniques involving the use of cervical skin flaps are multistaged and usually create a lumen of inadequate size. Other procedures, such as a free skin graft over tantalum and thoracic skin flaps, are only of historical interest. Similarly, the tubed deltopectoral flap described by Bakamjian[1] has also fall-

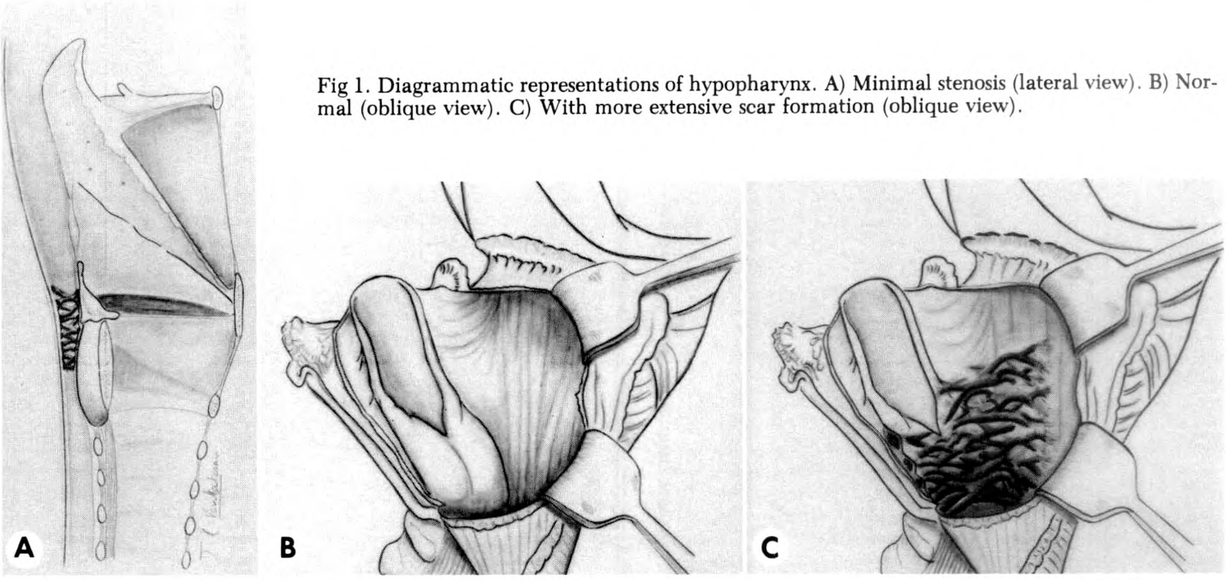

Fig 1. Diagrammatic representations of hypopharynx. A) Minimal stenosis (lateral view). B) Normal (oblique view). C) With more extensive scar formation (oblique view).

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Presented in part at the meeting of the American Laryngological Association, Palm Beach, Florida, April 28-29, 1990.

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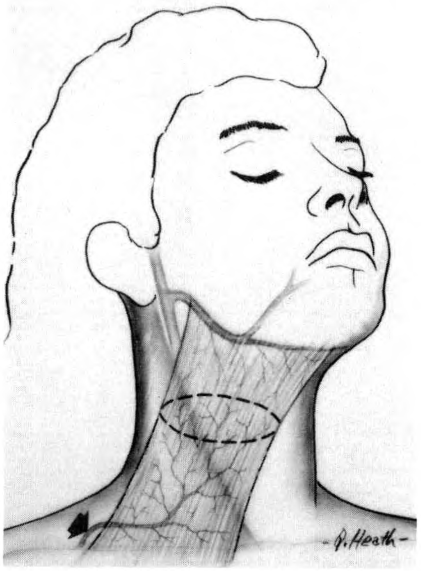

Fig 2. Inferiorly based flap supplied by superficial branch of transverse cervical artery.

en out of favor, as it involves a staged approach and carries a significant postoperative complication rate.

Gastric pull-up, colon interposition, and free jejunal transplant are all accepted methods of esophageal reconstruction,[2] but they are not a substitute for hypopharyngeal reconstruction that is associated with esophageal injuries. Similarly, they are not warranted for isolated hypopharyngeal reconstruction for two reasons. They are difficult procedures with significant morbidity, and often they do not provide adequate width to create the funnel-like function of the hypopharynx.

In well-selected cases, a tongue flap and dermal graft in a one-stage operation has yielded good results without the problem of fistula formation.[2] The pectoralis major myocutaneous flap largely replaced other flaps for one-stage reconstruction of the hypopharynx and cervical esophagus. The advantages include a superior blood supply and single-stage reconstruction. Although the postoperative fistula rate is high, most of the fistulas are self-limiting and require only conservative wound care. Because of annular closure, stenosis is a major problem at the distal anastomosis. The hair-bearing skin in many male patients poses other restrictions to the use of the flap. The major drawback, however, is the bulkiness of the flap, especially in women with large breasts and in men with well-developed pectoralis major muscles. Attempts to solve this problem have included the incorporation of random segments of skin with the pectoralis major myocutaneous flap and skin-grafted pectoralis major muscles. Trapezius and latissimus dorsi myocutaneous flaps have been used without any significant advantage over the pectoralis major myocutaneous flap.

Revascularized free fasciocutaneous flaps are thin, pliable, and permit careful contouring, which is particularly useful in the difficult distal anastomosis. This autograft can be used in the reconstruction of both circumferential and subtotal pharyngeal defects. The vascular pedicle is long and of relatively large diameter, allowing easy revascularization. The distance of the donor site from the head and neck area permits a two-team approach, thereby minimizing operative time. The advantages of one-stage reconstruction, minimal hospitalization, and potentially lower morbidity make this technique applicable to medically compromised patients.[3]

The search for a satisfactory hypopharyngeal reconstruction procedure has led us to use the platysma myocutaneous flap with considerable success. Our previously reported work with the inferiorly based platysma myocutaneous flap for reconstruction of the hypopharynx after cancer operations has demonstrated its suitability.[4]

The platysma is a unique muscle lying within the subcutaneous tissue. As a type 2 muscle, the platysma has two major vascular pedicles. The superiorly based flap has been used extensively for oral reconstruction and is based on the facial artery and vein.

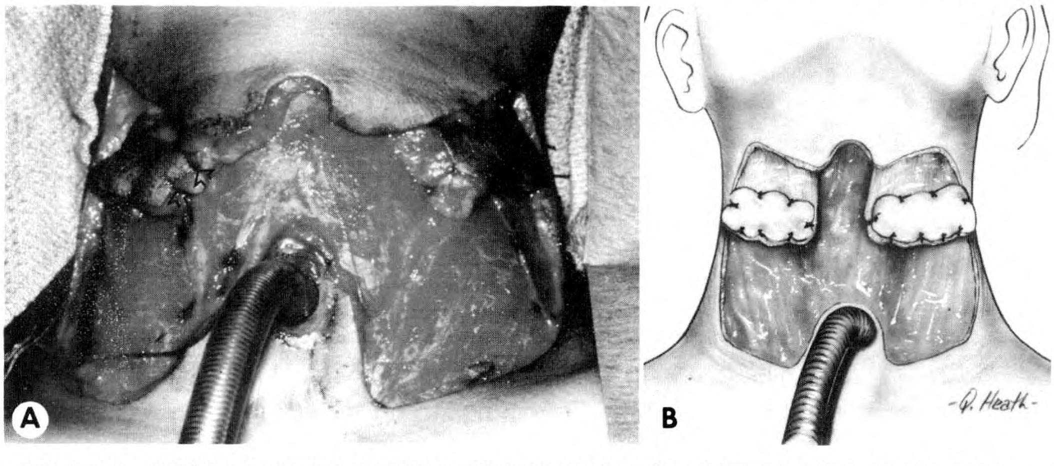

Fig 3. (Case 2) Bilateral superiorly based flaps. A) Arrows indicate how skin is sutured to underlying platysma to avoid shearing of skin away from muscle. (Flaps are retracted upward.) B) Illustration of flaps.

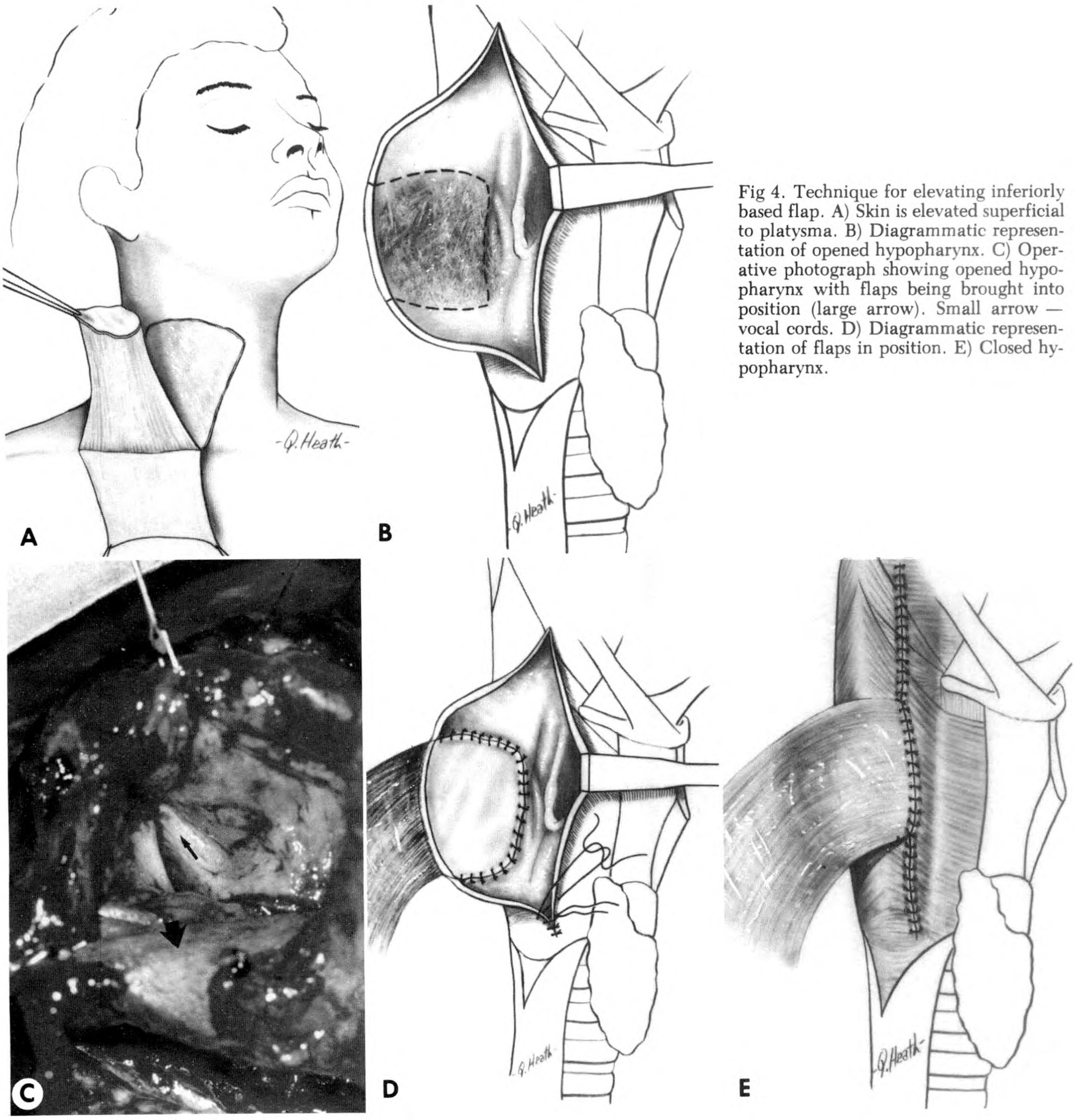

Fig 4. Technique for elevating inferiorly based flap. A) Skin is elevated superficial to platysma. B) Diagrammatic representation of opened hypopharynx. C) Operative photograph showing opened hypopharynx with flaps being brought into position (large arrow). Small arrow — vocal cords. D) Diagrammatic representation of flaps in position. E) Closed hypopharynx.

Its use for hypopharyngeal reconstruction has not been reported in detail. The technique for elevation of the superior flap has been previously described.[5,6] The inferior flap is based on the superficial branch of the transverse cervical artery (Fig 2). In addition, it receives numerous extremely fine muscular perforators from the sternocleidomastoid, trapezius, and strap muscles.[5-8] In contrast to the multiaxial arterial supply, the venous drainage appears to have a predominantly vertical orientation. Including a major superficial vein such as the anterior jugular, the external jugular, or the communicating vein with the flap may facilitate venous drainage.[6]

The platysma flap has several advantages over other myocutaneous flaps. It is local, the donor site is closed primarily, and with careful elevation the procedure is relatively simple, effective, and highly reliable. The operating time is shortened, as the procedure does not involve repositioning the patient or surgical manipulation of distant sites. The main advantage is that the flap is thin enough to permit satisfactory reconstruction without excess bulk.

In developing the flap, consideration must be given to the male beard pattern. In these cases, the skin island must be obtained from the inferior neck; hence, the inferiorly based flap is ideal.

Contraindications to this technique include previous radical neck dissection, which leaves the platysma scarred, fibrotic, and devoid of a reliable

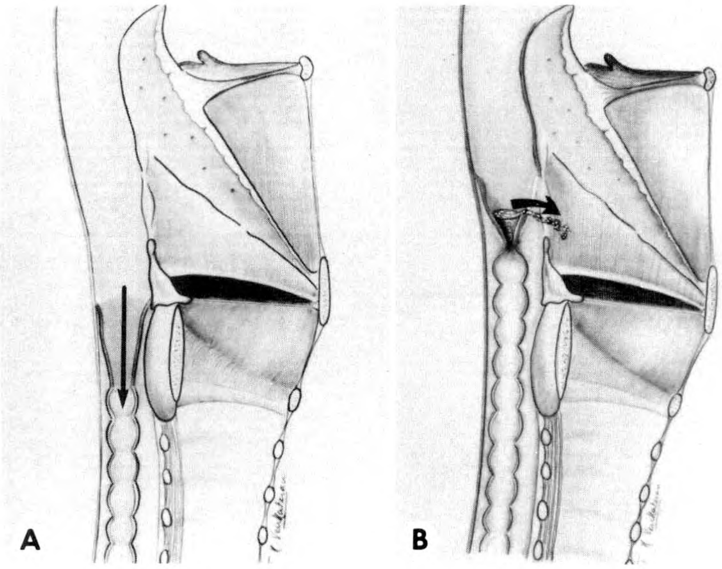

Fig 5. Bowel anastomosis. A) Proper level of bowel anastomosis to hypopharynx below level of cricoid. This creates functioning funnel system (arrow). B) Anastomosis above level of cricoid creates nonfunctioning funnel with spillover into larynx (arrow).

blood supply. Similarly, previous irradiation of the neck precludes the use of this flap because of the resulting skin changes and arteritis. Furthermore, this flap should not be used on patients with prominent jowls, because the platysma may be underdeveloped. Ipsilateral facial nerve paralysis should also be excluded, as the muscle mass may be inefficient in providing vascular support to the overlying skin. The decision on whether to use the platysma can be made preoperatively by having the patient voluntarily grimace.[9]

PATIENTS AND METHODS

The platysma myocutaneous flap was used in three of our patients with hypopharyngeal burns that resulted from lye ingestion. Since the technique for elevation of the superior flap is well established,[5,6] the details will not be reviewed. One of our patients was a candidate for bilateral superiorly based flaps (Fig 3). As she was a woman, there was no problem with hair-bearing skin and her short neck allowed for a pedicle of reasonable length based on the superior vessels. In the other two patients, who had long necks, inferiorly based flaps were used to allow for a shorter, more direct pedicle.

The following describes the technique for elevating the inferiorly based flap. The limits of the anticipated skin island should be outlined on the basis of criteria of shape, the extent of the defect, and the arc of rotation. The skin island must be large enough (usually greater than 5 cm in diameter) to include an adequate number of perforating vessels from the platysma. To create the inferiorly pedicled flap, the superior incision is extended through the skin and platysma. The inferior incision is carried through the skin only down to the platysma muscle (Fig 4A). The skin superficial to the platysma is then elevated inferiorly to the clavicle. The muscle is immediately sutured to the subcutaneous skin of the flap with 3-0 chromic sutures (cutting needle) to avoid shearing and separation of the muscle from the skin. The platysma donor segment is then elevated from the superficial cervical fascia along with the skin island, with preservation of the branches of the transverse cervical artery. The pharynx is opened via a lateral pharyngotomy, and obvious scar tissue is excised (Fig 4B). The inferiorly pedicled myocutaneous island is subsequently rotated into the open hypopharyngeal defect. Excision of tissue is not always necessary, and sometimes incision of the lateral pharynx with interposition of the flap is adequate. The flap is secured in place with interrupted chromic sutures (Fig 4C-E). The superiorly based flap as described can similarly be used in selected cases if the neck is short and the stenosis does not extend below the cricoid level.

RESULTS

In all patients, the flaps remained viable and healed without fistula formation. All patients had neck scars that were not significantly worse than a scar from lateral pharyngostomy without a platysma flap. Two patients required subsequent esophageal replacement to complete their reconstruction. One patient had only mild esophageal stenosis and required no further operation. All patients had a variety of laser and laryngeal endoscopic procedures to create a functioning airway. All three patients have minimal residual hypopharyngeal stenosis. All patients are able to eat a normal diet without aspiration or other difficulties.

CASE REPORTS

Case 1. A 36-year-old woman with a history of schizophrenia was admitted following ingestion of lye in an apparent suicide attempt. Direct laryngoscopy revealed severe burns involving virtually the entire oral cavity, oropharynx, and hypopharynx. She was placed on a regimen of steroids and antibiotics. Over a period of 2 years, she underwent repeated dilation of esophageal and laryngeal stenoses. Laser lysis of oropharyngeal scars was slowly carried out. During this period, she was unable to swallow her saliva and had a pharyngotomy and a salivary fistula. She was nourished via a gastrostomy tube and retained a tracheostomy tube in place for 2 years. She finally underwent pharyngeal reconstruction with a left platysma myocutaneous flap. A second-stage reconstruction of her esophagus was carried out with colon interposition. Subsequently, she has been able to eat normally and has no significant stenosis.

Case 2. Following the ingestion of a caustic soda solution, a 20-year-old woman underwent direct laryngoscopy and bronchoscopy that revealed extensive oropharyngeal burns and a lesser degree of involvement of the endolarynx, trachea, and hypopharynx. She was given a course of steroids and antibiotics. Following esophagoscopy that revealed severe stricture, she developed signs of an acute abdomen necessitating exploratory laparotomy. A gastric perforation was detected and managed by debridement and gastrostomy. She also underwent a tracheostomy and repeated airway dilations for laryngeal stenosis. Our thoracic surgery service did not consider her a candidate for colon interposition because of the extensive hypopharyngeal scar that would not allow tissue for anastomosis. She therefore underwent reconstruction with bilateral superiorly based platysma myocutaneous flaps. Six months later she underwent colon interposition with anastomosis to the distal flap. Currently, she eats normally and has adequate laryngeal function.

Case 3. A 24-year-old woman ingested lye in a suicide attempt. Initial treatment at another institution included tracheostomy and gastrostomy. Triple endoscopy revealed extensive burns of the supraglottic larynx and hypopharynx. There was almost complete destruction of the epiglottis, and laryngeal scar tissue developed. Significant scar tissue developed in both pyriform sinuses and in the postcricoid area. The patient was unable to swallow even saliva. Nine months after the injury her hypopharynx was reconstructed by relining the posterior wall with a platysma myocutaneous flap. Three weeks postoperatively the patient was able to swallow semisolid foods with no significant aspiration. The patient currently eats with no difficulty.

DISCUSSION

Hypopharyngeal stenosis must be recognized as an independent problem in dealing with the multiple complications of lye ingestion. Often, hypopharyngeal injuries are thought of as part of laryngeal or esophageal injuries when actually the focus of treatment is completely different. Hypopharyngeal burns are rarely isolated, so that associated treatment of the larynx or esophagus is essential to recovery. If esophageal replacement is not needed, reconstruction can be limited to the platysma flap as used in one of our patients. If esophageal replacement is planned, this will not obviate the need for hypopharyngeal reconstruction. Anastomosis must be accomplished below the level of the cricoid (Fig 5A). Anastomosis above the cricoid leads to a nonfunctional hypopharynx. The hypopharynx serves as the mouth of a funnel, whereas the esophagus serves as the stem. Attempts to anastomose colon or jejunum to the pharynx above the level of the cricoid lead to a nonfunctioning funnel system that causes spillover into the larynx and permanent problems with dysphagia and aspiration (Fig 5B).

The first step, therefore, in treatment of hypopharyngeal strictures is to identify the extent of the injury to this area and separate it from the laryngeal and esophageal injury. Alternatives for treatment are limited, as discussed. Other myocutaneous flaps are too bulky and difficult to use. A free flap is an excellent alternative, but much more difficult and no more reliable. The platysma myocutaneous flap is a relatively simple and reliable alternative that is within the capability of every head and neck surgeon.

CONCLUSION

Hypopharyngeal strictures can occur as an isolated problem or in association with laryngeal and esophageal strictures following lye ingestion. In either case, extensive stricture formation requires reconstruction to create a functional funnel system that empties below the cricoid. The platysma myocutaneous flap offers this reconstruction with a relatively simple, reliable, effective technique.

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Ann Otol Rhinol Laryngol 99:1990

ENDOSCOPIC MANAGEMENT OF EARLY SUPRAGLOTTIC CANCER

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An initial endoscopic surgical approach to early supraglottic cancer provides the surgeon with the ability to accurately stage these lesions, avoiding possible undertreatment while allowing for a valuable treatment option for those supraglottic cancers with histologically incontrovertibly superficial disease. Early invasion of the preepiglottic and paraglottic spaces can be determined accurately without altering or delaying any treatment option (open surgical excision, radiotherapy, or chemotherapy). The tendency of supraglottic cancers to transgress the natural foramina of the epiglottis is well established, and the concern about this depth of invasion is reflected by the 1977 revised staging criteria, which required assessment of the preepiglottic space (PES). Along with the microscope and the carbon dioxide laser, the adjustable supraglottiscope facilitates the determination of PES invasion and facilitates en bloc excision of superficial supraglottic cancers. The resulting morbidity typically is no different from that with routine direct endoscopy and biopsy.

KEY WORDS — epiglottis, laryngeal cancer, laryngeal staging, laryngoscopy, laser, supraglottic cancer.

INTRODUCTION

Most early aerodigestive tract cancers are easily treated by any conventional method. Even endoscopic excision of supraglottic cancer is successful when the cancer is early enough. Therefore, which cancer is early and which cancer is not early becomes the critical question, and depth of invasion is felt to be a major factor in this determination. This concern about depth of invasion is reflected by the additional requirement in the 1977 American Joint Committee criteria for staging of supraglottic cancer to assess cancer invasion into the preepiglottic space (PES).[1] However, depth of cancer invasion in the supraglottis is often difficult to discover. It is especially so in the area of the infrahyoid epiglottis, where apparently early cancers may easily invade the PES through natural foramina. Because direct laryngoscopy, computed tomography (CT), and magnetic resonance imaging are ineffective in detecting early PES invasion, surgical exploration of this space has become an essential component in the management of these patients. Open laryngectomy will usually both treat and determine extent of the disease; however, even very early supraglottic cancers may require tracheotomy and subject the patient to the risks of aspiration and the morbidity of an open procedure.

That surgical exploration of early supraglottic cancers can be performed transorally and thus one can avoid much of the morbidity associated with open procedures was demonstrated over 50 years ago by Jackson and Jackson, who used a punch biopsy forceps to cut around selected suprahyoid epiglottic cancers. They performed a microscopically controlled excision, and if there was no cancer in the punch specimens, the excision was considered curative.[2] However, because of difficult instrumentation and poor visualization, this approach was not suitable for infrahyoid cancers. Since the 1930s, this has remained the standard for endoscopic management of early supraglottic cancer.

In the late 1950s the operating microscope was introduced to laryngology.[3-5] Improved lighting systems for the microscope and laryngoscopes were developed in the 1960s and 1970s. The carbon dioxide (CO_2) laser was introduced by Jako[6] and Strong and Jako[7] for microlaryngeal surgery in 1972. The superb visualization and precision of the CO_2 laser and the operating microscope allowed expansion of Jackson and Jackson's old concept. In 1978, Vaughan[8] described endoscopic laser resection of various supraglottic structures, including the epiglottis and false vocal folds both in the dog model and in selected cases of supraglottic cancer.

Davis et al,[9] in 1983, discussed the first series of patients undergoing laser epiglottectomy. Indications included staging in six patients, treatment of malignant disease in four patients, and treatment of benign epiglottic lesions in four patients. The procedure was originally performed with a Lynch laryngoscope system (Baxter Corp, V Mueller Division, catalog numbers BE 850, 860, and 865). This system provided good access to the surgical field. However, because the Lynch system has no self-contained light source and is without an inferior laryngoscope blade to prevent the endotracheal tube from displacing anteriorly into the operative field, visualization remained poor. Because of these problems, during the 1980s, laser epiglottectomy was

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Presented at the meeting of the American Laryngological Association, Palm Beach, Florida, April 28-29, 1990.

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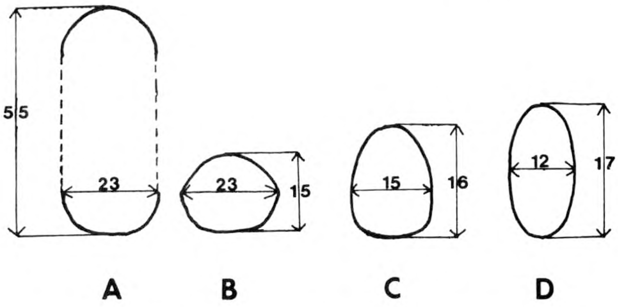

Fig 1. Distal dimensional working areas in millimeters. A) Adjustable supraglottiscope (closed). B) Adjustable supraglottiscope (full separation and distension). C) Jako laryngoscope. D) Dedo laryngoscope.

performed exclusively with large-bore tubed laryngoscopes such as the Jako (Pilling Co, catalog number 52-2206). At the American Laryngological Association meeting in 1988, Zeitels et al[10] discussed the indications and technique for 50 epiglottectomies using the CO2 laser through tubed laryngoscopes. The procedure took approximately 2 hours, it required frequent repositioning of the laryngoscope, and the epiglottis seldom could be removed in one piece. Laser epiglottectomy was felt by some to be beyond the scope of those with standard laryngoscopic skills.[11]

The problem was that of exposure. Laryngoscopes designed for glottic surgery are longer than necessary and are too narrow to reveal the entire supraglottic surgical field. Therefore, an adjustable supraglottiscope with short, wide blades and distal lighting was developed.[12] It has clip-on tubes to remove laser effluent. The working area of this adjustable supraglottiscope is triple that of tubed laryngoscopes and reveals the entire supraglottis (Fig 1).

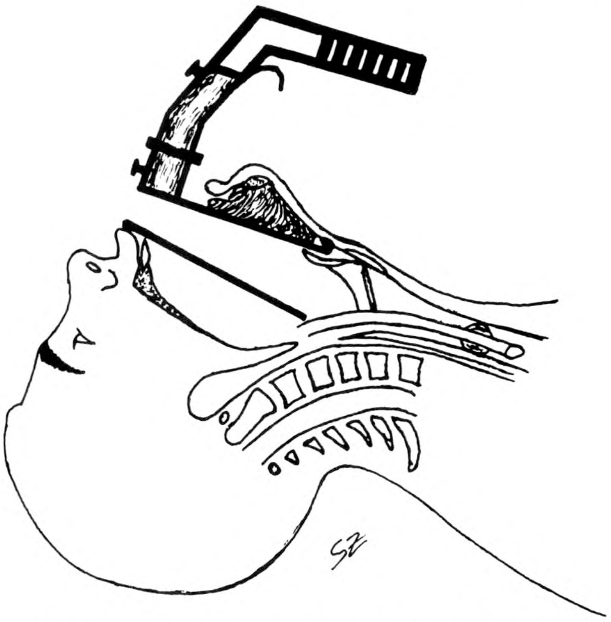

Fig 2. Schematic representation of adjustable supraglottiscope in position with upper blade in vallecula and patient in suspension. (From Zeitels and Vaughan.[12] Reprinted with permission.)

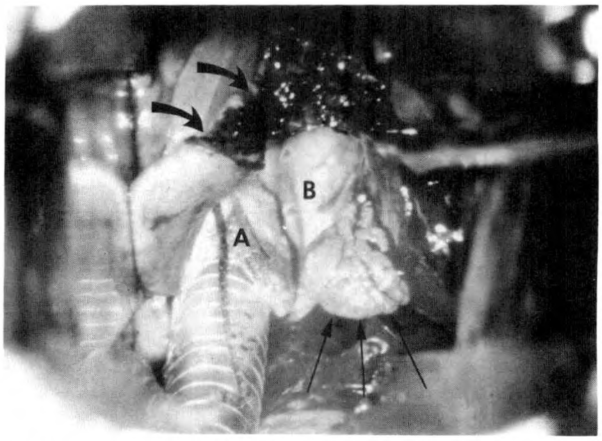

Fig 3. (Case 1) Exophytic carcinoma of right aryepiglottic fold (thin arrows). Epiglottis has been incised sagittally in midline (heavy arrows), and right supraglottis is folded open. A — cottonoid protecting endotracheal tube, B — right false vocal cord.

This wide exposure and the fact that instruments may be introduced at an angle between the blades of the laryngoscope allow the surgeon to retract tissues within the large surgical field, thereby altering the operative site without repositioning the laryngoscope. En bloc excision of early supraglottic lesions can now be performed easily, quickly, and, we believe, by the average surgeon. The resulting morbidity typically is no different from that with routine direct endoscopy and biopsy. The resulting information may profoundly influence management of the cancer.

SURGICAL TECHNIQUE

Endotracheal anesthesia is maintained through a foil-wrapped, red rubber endotracheal tube that is further protected from laser impaction by wet cottonoid. The supraglottiscope is inserted with the blades closed. The blades are placed to best reveal the area in question (Fig 2[12]). With a lesion on the epiglottis or on the aryepiglottic fold (Figs 3-6), the superior blade is placed in the vallecula. After the

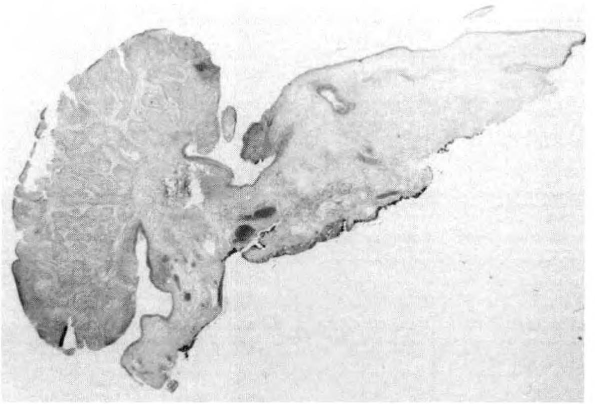

Fig 4. (Case 1) Histologic section through resected specimen revealing well-differentiated microinvasive squamous cell carcinoma (H & E).

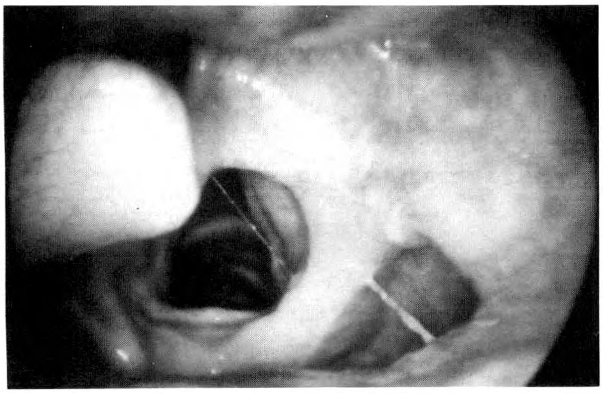

Fig 5. (Case 1) Clinical photograph taken during inspiration through rigid telescope 1 year postoperatively.

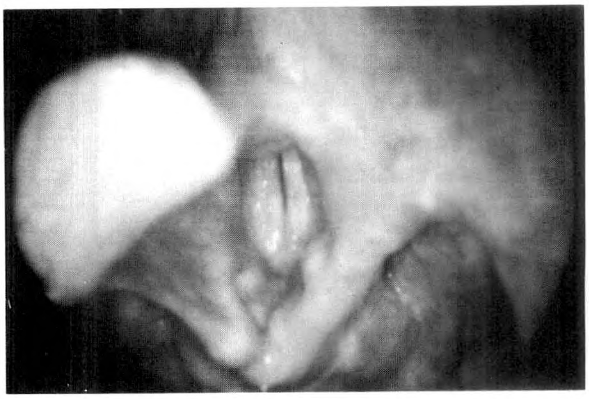

Fig 6. (Case 1) Clinical photograph taken during phonation through rigid telescope 1 year postoperatively.

scope is positioned, the blades are fully separated and the inferior blade is additionally distended. This action retracts the endotracheal tube into the interarytenoid space and out of the operative field. The scope is held in position by the Boston University Suspension (Pilling Co, catalog number 50-2260).

The precise location of the tumor is noted and documented on an anatomic map. The surface dimensions are measured and recorded. Depth of tumor invasion is first assessed by careful palpation with a blunt probe or suction (velvet eye) for evidence of bulk and by checking for movement of the tumor over the underlying structures. An excisional biopsy is attempted if the tumor appears to be an early one (small enough to get around peripherally), or PES exploration is performed if the cancer's depth is uncertain, as it often is with carcinoma involving the infrahyoid epiglottis.

In performing epiglottectomy, the vallecular mucosa and the underlying hyoepiglottic ligament are incised and the dissection is continued along the anterior surface of the epiglottis in the PES. If the CO_2 laser and the operating microscope are used, gross cancer, when present, can be visualized easily and sampled for biopsy. If cancer is documented in the PES, the endoscopic procedure is terminated and either definitive open laryngectomy is performed or radiotherapy is administered. The type of laryngectomy is individualized to the patient and the extent of the disease.

If there is no indication of PES invasion, the excisional biopsy is completed by removal of as much of the epiglottis and adjacent false vocal folds and/or aryepiglottic folds as is necessary to encompass the lesion. Determination of the margins is guided by visualization of the dry surgical field with the surgical microscope and is aided by frozen section evaluation of the patient margins. Hemostasis is obtained with electrocautery or a defocused laser spot. No effort is made to close the wound; it heals by secondary epithelialization. The postoperative airway is protected by preoperative corticosteroid (dexamethasone sodium phosphate 10 mg intravenously), and tracheotomy is not required. On recovery from anesthesia, analgesics are not needed and normal alimentation is encouraged. H_2 receptor antagonists and antacids are administered to patients with a history of reflux.[10] Final determination of the adequacy of the excision is made only after examination of the permanent histologic sections from the resected specimen. If they are clear and if the cancer has not been pathologically staged as T3, it is not further treated.

REVIEW OF CASES AND RESULTS

Between 1983 and 1989, 22 patients were clinically staged with T1 or T2 supraglottic cancer. None of these patients showed PES invasion by CT scan. After laser epiglottectomy, 7 of the 22 (32%) patients were found to have invasion through epiglottic fenestrations into the PES. They were upstaged to a T3 diagnosis and underwent conventional open laryngectomy.

The adjustable supraglottiscope was used on five patients with supraglottic cancer during the period October 1988 through December 1989. Four patients underwent en bloc excisional biopsy of early supraglottic cancer (see Table). Clear margins were obtained in all patients by permanent sections from a single operative specimen. None of the four had invasion of the PES; therefore, none were staged beyond T1. They had no further treatment and there have been no local recurrences.

The fifth patient had a large T3 supraglottic cancer shown with CT scan and endoscopic evidence of extensive PES invasion. Despite vigorous encouragement, he refused any form of open surgical treatment. He underwent a transoral, en bloc supraglottic laryngectomy that included both false cords, the epiglottis, and most of the PES and upper paraglottic spaces (Figs 7-10). We considered this to be a large excisional biopsy. Although there were clear surgical margins on the resected specimen, both sides of the neck remained at risk; the patient was further treated with full-course radiotherapy to the

THERAPEUTIC LASER SUPRAGLOTTIC RESECTION WITH ADJUSTABLE SUPRAGLOTTISCOPE

Case	*Stage*	*Site*	*Follow-up (mo)*	*Surgical Margins*	*Radiotherapy*	*Present Status*		*Aspiration*
						Larynx	*Neck*	
1	T1	AEF	24	Clear	–	NED	NED	–
2	T1	FVC	20	Clear	–	NED	NED	–
3	T3	Epi	17	Clear	+	NED	Rec*	5 wk
4	T1	Epi	16	Clear	–	NED	NED	–
5	T1	Epi	10	Clear	–	NED	NED	–

AEF — aryepiglottic folds, FVC — false vocal cords, Epi — epiglottis, NED — no evidence of disease, Rec — recurrence.

*This patient had received full-course radiotherapy to primary site and both sides of neck. After extended discussion, patient consented to and underwent left radical neck dissection.

primary site and both sides of the neck. Since completing his radiotherapy, the patient has had two direct endoscopies that have shown no evidence of recurrence at the primary site.

All patients healed by secondary epithelialization, and there have been no episodes of local infection or chondritis. No patient required a tracheotomy. The patient who had endoscopic subtotal laryngectomy had aspiration that resolved over 5 weeks.

DISCUSSION

The operating microscope, the CO2 laser, and the adjustable supraglottiscope provide the head and neck surgeon with the tools to separate clearly and easily those patients with superficial cancer in the supraglottis from those with deep invasion.

The importance of deep invasion of supraglottic cancer was discussed extensively at the Centennial Conference on Laryngeal Cancer in 1974. The frustration in evaluating the "invisible third dimension" of PES invasion was voiced by Dr D. Harrison: "What you are saying is fine looking at three dimensional sections, but what practical importance is it because you can't detect it until the larynx is cut?" He further stated, "Well,.......there is a space, it can be called lots of things, and this space is important because it's a way in which tumors can get into a region in which there is bilateral spread to the neck glands which we all know is a problem. It is a space involvement of which is not too easy to be certain as to whether there is invasion." Dr Bridger subsequently commented, "We're interested in where the cancer is when it's at the early T1 and T2 stage because this is when the modalities of treatment really matter."[13] The consensus was that tumors invading the preepiglottic region portend a worse prognosis. Subsequently, in 1977, the American Joint Committee on Cancer assigned a T3 classification to supraglottic cancer with PES involvement.[1,14]

Although radiographic imaging has helped evaluate the PES, it is not a sensitive modality for evaluating early invasion of this area (Fig 11). Our epiglottectomy series reveals that 7 of 22 patients (32%) were found to have occult PES invasion not detectable by CT scan. In a smaller series, R. K. Davis et al (unpublished data, 1990) reported an identical figure of 33%. Therefore, most surgeons have agreed with Harrison and cut the larynx in order to explore the space. This of course resulted in some form of open laryngectomy.

If as a result of endoscopic exploration there is no PES invasion found, and the process results in an en bloc excision of an early lesion with clear surgical margins, the tumor has been separated from the patient and no further therapy is indicated. The route of the exploration should not matter, be it open or transoral. In our experience with the transoral route, there have been no local recurrences when

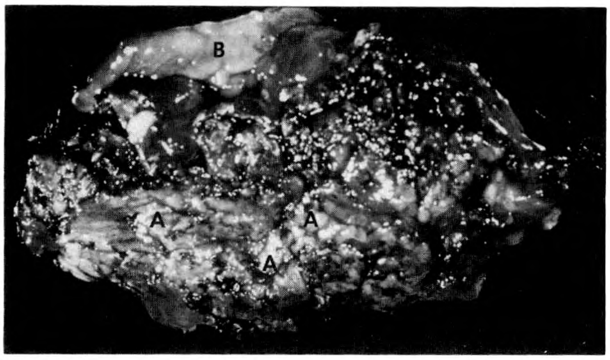

Fig 7. (Case 3) Gross specimen as viewed anteriorly (deep margin). A — normal preepiglottic fat, B — tip of epiglottis with normal vallecular mucous membrane.

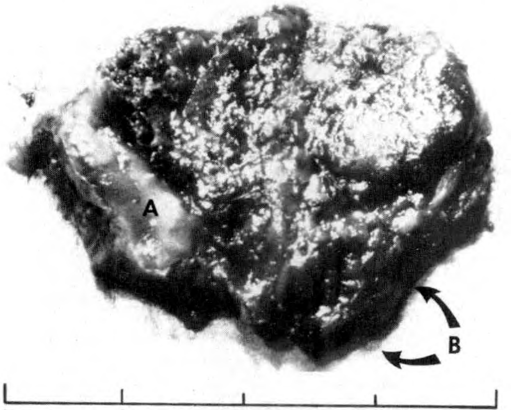

Fig 8. (Case 3) Gross specimen as viewed posteriorly (laryngeal surface). Specimen was 5 cm in diameter. A — normal mucous membrane on left lateral margin and left false vocal cord, B — normal mucous membrane of right false cord and inferior margins is obscured by exophytic nature of cancer.

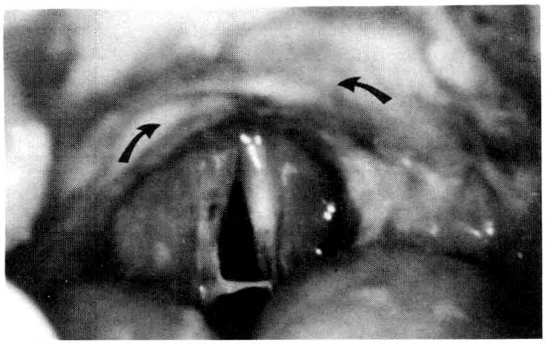

Fig 9. (Case 3) Clinical photograph taken through rigid telescope 5.5 months postoperatively and 2 months after radiotherapy. Arytenoids are edematous, and there are no false vocal cords. Thyroid cartilage is covered by inflamed mucous membrane (arrows).

permanent evaluation of the main specimen reveals clear margins. We have seen no local recurrences in this current series with short follow-up or in our previously reported series of seven patients with a 38-month median follow-up.[10]

If the exploration of an apparently early cancer reveals deep invasion, the patient is no longer at risk for undertreatment. Treatment appropriate to the patient and the true extent of disease may begin without delay, be it partial, near-total, or total laryngectomy and/or radiotherapy. If the exploration is done transorally at the time of endoscopy, the patient may be appropriately informed about the need for such treatment prior to its performance. An open surgical procedure performed primarily to guard against the possibility of preepiglottic invasion is no longer needed.

Other advantages of successful endoscopic excision of early supraglottic cancer include short operating time, no voice change except improvement if a bulky lesion is removed, no tracheotomy, no aspiration when superficial disease is removed, prompt discharge home the day after operation, and early resumption of a normal life-style.

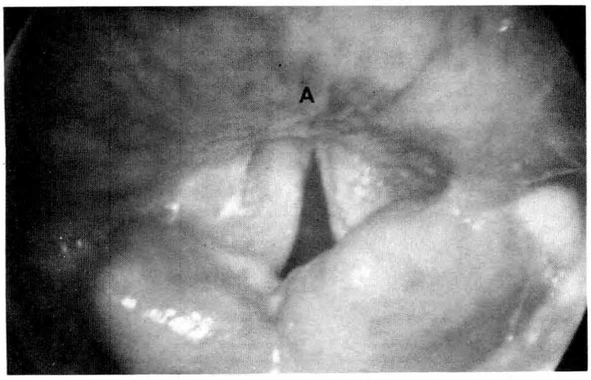

Fig 10. (Case 3) Clinical photograph taken through rigid telescope 8.5 months postoperatively and 5 months after radiotherapy. Patient continues to have anterior granulation and circumferential cicatrix, forming new supraglottic valve. A — anterior mucous membrane is now smooth and well healed.

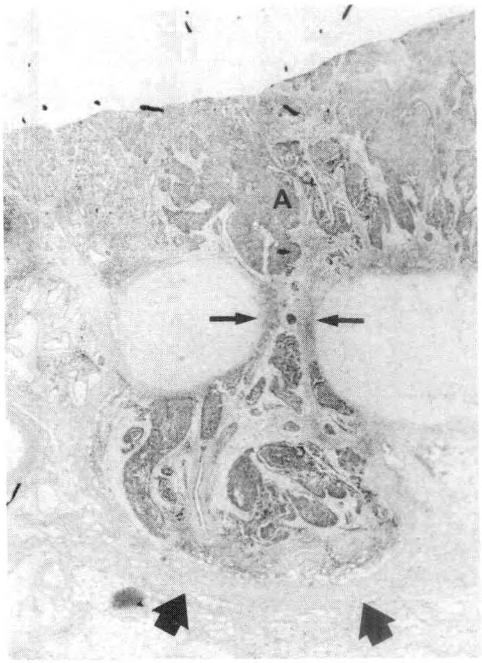

Fig 11. Carcinoma on laryngeal surface of epiglottis (A) growing through natural epiglottic fenestration (thin arrows) into preepiglottic space. Typical fibroelastic pseudocapsule has formed (heavy arrows) around advancing cancer.

Endoscopic resection of early supraglottic cancer should be a part of the normal armamentarium of treatment options that includes supraglottic laryngectomy, near-total laryngectomy, total laryngectomy, and radiotherapy. It is not a replacement for any of these established treatment modalities.

CONCLUSIONS

Endoscopic management of early supraglottic cancer is the only effective method to determine accurately which cancers are early and which are not before definitive therapy. This approach has been facilitated by technologic developments over the last 35 years and should be employed in any patient with an apparently early supraglottic cancer who can undergo endoscopy. Endoscopic exploration may provide important staging information and can do so without altering established treatment options. It also provides the head and neck surgeon with a valuable treatment alternative for those supraglottic cancers that are histologically incontrovertibly early.

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NEUROLARYNGOLOGY SYMPOSIUM

A Neurolaryngology Symposium will be held on July 21, 1991, at the Warwick Hotel in Philadelphia, Pennsylvania. For further information, contact The Voice Foundation, 1721 Pine St, Philadelphia, PA 19103; (215) 735-7999.

Ann Otol Rhinol Laryngol 99:1990

BILATERAL SEMICIRCULAR CANAL APLASIA WITH NEAR-NORMAL COCHLEAR DEVELOPMENT

TWO CASE REPORTS

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Congenital malformations of the vestibular labyrinth (pars superior) are rare. We present two patients with computed tomographic findings of bilateral semicircular canal aplasia with normal or near-normal cochleas. Initial bone conduction thresholds were within normal limits, although both patients had significant conductive hearing losses due to congenital middle ear malformations. Bithermal caloric responses were absent in both. To our knowledge these are the first reports of vestibular aplasia concomitant with normal or near-normal cochlear development. These findings conflict with conventional hypotheses that state that inner ear malformations result from arrested development during the normal stages of inner ear embryogenesis.

KEY WORDS — congenital inner ear malformation, inner ear embryology, semicircular canal aplasia.

INTRODUCTION

Embryology mirrors phylogeny. This maxim emphasizes the direct relation between a structure's phylogenetic age and its resistance to developmental abnormalities.[1]

During inner ear embryogenesis, the membranous labyrinth divides into the pars superior and the pars inferior. The pars superior gives rise to the three semicircular canals, the utricle, and the endolymphatic duct. The pars inferior goes on to form the cochlea and saccule. Since the pars superior is phylogenetically older, it develops earlier than the pars inferior in the ontogeny of the embryo and should be more resistant to developmental defects.[2]

Discussions attempting to explain inner ear abnormalities have centered around this hypothesis that malformations result from arrested development during the normal stages of inner ear embryogenesis.[3] The following two cases of vestibular aplasia concomitant with normal or near-normal coch-

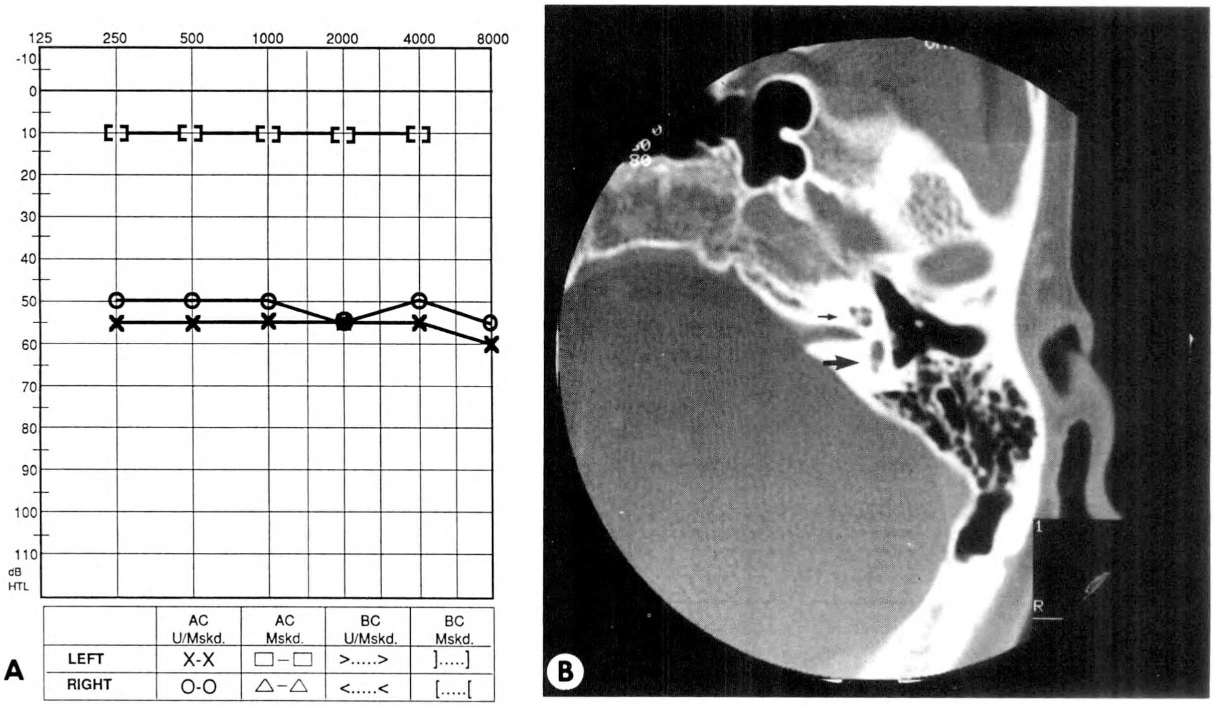

Fig 1. (Case 1) A) Audiogram at 5 years of age. Note normal bone conduction thresholds in both ears. B) Axial computed tomogram of left temporal bone. Vestibule appears mildly dilated (large arrow). Note normal cochlea (small arrow) and complete absence of semicircular canals. Findings were identical in right temporal bone.

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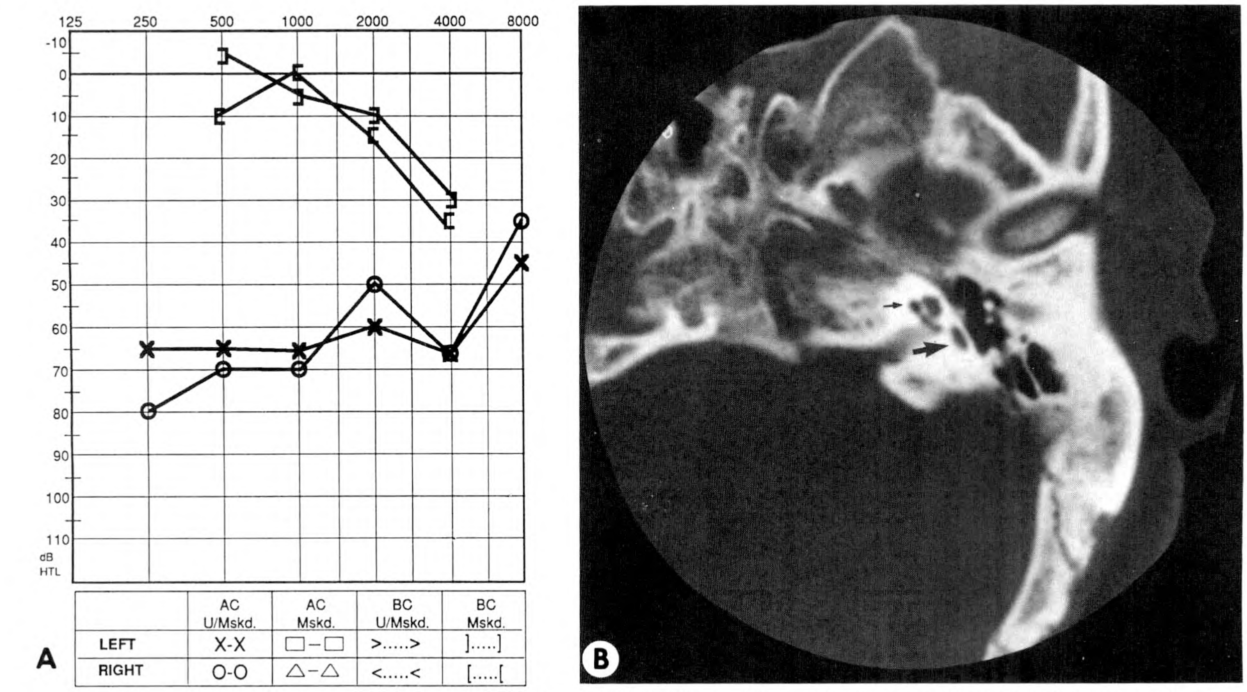

Fig 2. (Case 2) A) Audiogram at 9 years of age. Note marked conductive losses and near-normal bone conduction pure tone averages in both ears. B) Axial computed tomogram of left temporal bone. Vestibule appears normal (large arrow). There is mild dilatation of cochlear lumen (small arrow). Note complete absence of semicircular canals. Findings were identical in right temporal bone.

lear development conflict with this conventional hypothesis.

CASE REPORTS

Case 1. A 27-year-old mentally retarded woman originally presented elsewhere at age 5 with hearing loss and delayed speech. The audiogram revealed a bilateral conductive hearing loss (Fig 1A). She underwent a left stapedectomy at age 8 and a right stapedectomy at age 10. Both middle ears had a congenitally fixed footplate and a rudimentary incus. Postoperative hearing results remained unchanged in both ears.

She was lost to follow-up until 1988, when she presented for reevaluation of her hearing loss. Findings on the physical examination were unremarkable except for a slitlike right external auditory canal. Audiometry at this time revealed a bilateral conductive hearing loss. Bithermal caloric responses were absent. The temporal bone computed tomography (CT) scan showed mild bilateral vestibule dilatation with absent semicircular canals (Fig 1B). The cochleas were normal, albeit with obliterated oval and round windows. Treatment consisted of upgrading her binaural amplification.

Case 2. A 32-year-old woman originally presented in childhood with a congenital hearing loss. She was late in walking because of balance difficulties that have persisted to the present time. At age 8 she entered a school for the deaf. An audiogram at that time demonstrated bilateral maximal conductive hearing losses with a mild sensorineural component (Fig 2A).

On her return in 1989 for reevaluation of her hearing loss, the audiogram showed a bilateral mixed loss. Caloric responses were absent bilaterally. The temporal bone CT scan revealed absence of the semicircular canals bilaterally. Both cochleas contained $2^1/_2$ turns, but were unusual in angulation, with compression in the base-to-apex dimension (Fig 2B). Treatment consisted of upgrading her binaural amplification.

DISCUSSION

In 1791 Mondini[4] described a case of congenital deafness. The gross findings revealed a cochlea with $1^1/_2$ turns and an incomplete interscalar septum. Alexander,[5] in 1904, first described the microscopic features of this anomaly. Prior to the 1950s, postmortem examinations were the only means available to diagnose congenital inner ear malformations. With the advent of newer imaging techniques, the term Mondini's dysplasia grew to encompass various anomalies of the osseous labyrinth.[6] In 1969 Valvassori et al[7] described the application of temporal bone polytomographic radiography. The technique offered visualization of desired structures while obscuring those in front and behind. With appropriate positioning, different projections lent themselves to the visualization of specific inner ear structures.

High-resolution CT scanning permits more reliable and precise descriptions of these disorders and has supplanted polytomography. It provides much better bony and soft tissue detail with a much lower radiation dose. Several reports using temporal bone CT imaging have described abnormalities of the cochlea, semicircular canals, and vestibular aqueducts alone or in combination.[3,6,8-10]

The pars superior, being phylogenetically older than the pars inferior, should be more resistant to developmental defects.[1] Bearing this in mind, one would be surprised to find two cases of near-total aplasia of the vestibular labyrinth with normal cochlear function. Paparella[1] noted total aplasia of the vestibular labyrinth in 5 of 12 patients with Mondini's dysplasia, but all had abnormal cochleas. Jackler et al[6] formulated a classification of inner ear malformations. Their compilation of 63 patients with 98 congenitally malformed ears is by far the largest series to date. They classified congenital inner ear malformations according to radiographic appearance. The classification consisted of two main groups: those with absent or malformed cochleas and those with normal cochleas. Each group was then subclassified according to other dysplastic characteristics. The lateral canal was the most commonly malformed semicircular canal. Superior semicircular canal abnormalities, although less common, were always associated with changes in the lateral semicircular canal. They reported no cases of total semicircular canal aplasia with normal cochleas. There have been other reports of normal cochleas with isolated lateral semicircular canal abnormalities.[1,7,9-12] To our knowledge, these are the first reports of total semicircular aplasia associated with normal or near-normal cochlear development.

The vestibular labyrinth and cochlea differentiate from the otocyst. The vestibular labyrinth begins differentiation during the sixth week, while the cochlea starts to differentiate during week 8. The semicircular canals begin as evaginating epithelial folds from the vestibule. Failure of these folds to form would yield complete absence of the involved semicircular canals. It is difficult to explain the existence of aplastic vestibular labyrinths with normal or near-normal cochleas on the basis of the arrested-development theory of congenital abnormalities. Arrested development at the time of vestibular differentiation should also lead to dysmorphology of the cochlea. Our two cases conflict with this conventional hypothesis and suggest a specific aberrant "place" lesion that does not arrest further development of other structures arising from a common primordium.

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Ann Otol Rhinol Laryngol 99:1990

EFFECTS OF CYCLOPHOSPHAMIDE ON THE PATHOGENESIS OF CYTOMEGALOVIRUS-INDUCED LABYRINTHITIS

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Cyclophosphamide was used in this study to define the contribution of the inflammatory response relative to direct cytopathic effects of guinea pig cytomegalovirus (GPCMV) in inducing sensorineural hearing loss in the guinea pig. The eighth nerve compound action potential (CAP) threshold on day 7 after inoculation of GPCMV into the scala tympani was an average of 35 dB greater for control animals than for those that were immunosuppressed with daily intraperitoneal injections of cyclophosphamide (20 mg/kg body weight). The amount of GPCMV antigen in the cochlea, detected immunohistochemically, did not correlate with the CAP threshold. However, the greater the inflammatory response to GPCMV in the cochlea, the higher the CAP threshold and thus the greater the hearing loss. This study demonstrates that the inflammatory response to GPCMV may be more important than direct cytopathic effects of the virus in producing sensorineural hearing loss in GPCMV-induced labyrinthitis.

KEY WORDS — cochlea, immunosuppression.

Cytomegalovirus (CMV) is the most common human congenital infection, occurring in approximately 1% of newborns.[1,2] Sensorineural hearing loss (SNHL) is found by age 2 in approximately 20% to 65% of those with cytomegalic inclusion disease,[3-8] and is the single most important abnormality to develop in those born with asymptomatic congenital CMV infection.[3,9-17] Overall, at least 4,000 children annually (1 in 750 live births) are estimated to manifest SNHL from CMV infection to a degree that impairs learning and verbal communication.[3,13,18]

The first direct evidence linking CMV with cochlear disease came from histologic temporal bone studies of eight infants with congenital CMV infection.[8,13,19-22] Cytomegalovirus inclusions were found throughout both the cochlear and vestibular endolymphatic ducts, and an anticomplementary immunofluorescent technique in two cases[13] revealed viral antigen in cells of the organ of Corti and the neurons of the spiral ganglion. In some cases, edema and inflammation in the vestibule and cochlea were more impressive than viral cytopathology, prompting Stagno et al[13] to speculate that immune-mediated damage to inner ear neurosensory structures may be as important as or more important than viral destruction in CMV labyrinthitis.

Studies of hearing loss associated with infection of the guinea pig cochlea with guinea pig CMV (GPCMV) provided further evidence that immune mechanisms may contribute to inner ear damage in CMV labyrinthitis.[23,24] Inoculation of GPCMV into the scala tympani of seronegative guinea pigs resulted in profound deafness after 8 days. The earliest morphologic change in the cochlea following inoculation with GPCMV was infiltration of inflammatory cells into the cochlear duct and adjacent structures,[25] before the appearance of cytomegalic inclusions[26] or hearing loss.[25] Serum or perilymphatic anti-GPCMV antibody did not appear by day 8 after inner ear[23] or systemic GPCMV inoculation[27]; hence, immune-mediated damage may have been due primarily to the cellular immune response. It was suggested that if the inflammatory process in the cochlea was halted before the onset of structural damage, the hearing loss might be prevented.[25]

Cyclophosphamide is a broad-spectrum immune and inflammatory modulator[28] that suppresses cell-mediated immunity in guinea pigs when given at a daily dose of 20 mg/kg body weight.[29-32] In this study, cyclophosphamide was used to define the effects of immunosuppression on hearing loss and histopathology in guinea pigs with GPCMV labyrinthitis.

MATERIALS AND METHODS

Animals. Two-month-old outbred Hartley guinea pigs (Crest Caviary, Raymond, Calif) weighing

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Presented at the meeting of the American Otological Society, Inc, Palm Beach, Florida, April 28-29, 1990.

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400 to 500 g were used in all experiments. Animals were tested for the presence of serum antibody to GPCMV, and only seronegative animals were included in studies of the effect of cyclophosphamide on the eighth nerve compound action potential (CAP) threshold and cochlear histopathology in guinea pigs with GPCMV labyrinthitis. Anesthetic (sodium pentobarbital [Nembutal] 30 mg/kg intraperitoneally [IP], and fentanyl and droperidol [Innovar-Vet] 0.3 mL/kg intramuscularly) was given before all experimental procedures.

Cytomegalovirus Antibody Assay. Serum samples were tested for the presence of antibody to GPCMV by an enzyme-linked immunosorbent assay (ELISA) that uses staphylococcal protein A conjugated with horseradish peroxidase (Zymed, Burlingame, Calif).[33] Stock preparations of GPCMV-infected and noninfected guinea pig embryonic fibroblasts were used as the antigens. The assay was performed in a 96-well microfiltration plate (V&P Enterprises, San Diego, Calif), and the absorbance in each well was read on a micro-ELISA reader with a 490-nm filter (Dynatech Laboratories, Alexandria, Va). A standard curve was constructed by testing a serum known to have a high antibody titer to GPCMV. A serum specimen, diluted 1:1,000 and 1:2,000, with absorbance values of >0.05 optical density was considered to be positive for anti-GPCMV antibodies.

Cyclophosphamide Treatment. Experimental animals received daily IP injections of cyclophosphamide (Mead Johnson, Evansville, Ind) at a daily-adjusted dose of 20 mg/kg body weight, equivalent to approximately 200 mg/m^2 body surface area per day. Control animals received an equal-volume daily-adjusted IP injection of sterile phosphate-buffered saline (PBS). Experimental guinea pigs were pretreated with cyclophosphamide for 6 days, then inoculated with live or inactivated GPCMV (see below) and continued on cyclophosphamide for an additional 7 days.

Virus. The GPCMV (American Type Culture Collection No. 22122) was originally provided by Drs B. P. Griffith and G. D. Hsiung of Yale University. Salivary gland suspensions containing 10^6 TCID$_{50}$/mL were prepared and stored in 75-µL aliquots at −70°C.[23] Each aliquot was thawed only once, immediately prior to use.

As a control for surgical technique and fluid injection (see below), the left ear of each animal was inoculated with inactivated GPCMV. Inactivated GPCMV was produced by mixing the salivary gland suspension with 10 µg/mL psoralen (4′-amino methyl-4,5′,8-trimethylpsoralen; Calbiochem-Behring, La Jolla, Calif) and exposing the mixture for 10 minutes to long-wave ultraviolet light.[34] The inactivated stock was divided into aliquots and stored at −70°C.

Auditory Nerve Recordings. The threshold for the eighth nerve CAP was measured by surgically opening the tympanic bullae and employing a round window electrode.[23,24] Measurements were made in each ear of both cyclophosphamide- and saline-treated guinea pigs on the day of virus inoculation (day 6 of treatment) and again just prior to killing the animals 7 days after inoculation.

Perilymphatic Inoculation. After baseline measurements of the auditory threshold were made, a hole (approximately 250 µm) was hand-drilled through the cochlear capsule of the basal turn into the scala tympani of each ear. Live GPCMV (25 µL, 10^6 TCID$_{50}$/mL) was injected with a glass micropipet into the scala tympani of the right ear, and 25 µL of inactivated GPCMV was injected into the left scala tympani. Previous experiments in this laboratory showed that live GPCMV placed in one inner ear does not spread to the other inner ear.[26] Each hole was then covered with bone wax, the wound was closed, and the animal was allowed to recover.

Cochlear Histopathology. Following the measurement of the CAP threshold 7 days after virus inoculation and the collection of blood and tissue samples (see below), animals were intracardially perfused with warm saline followed by 5% paraformaldehyde in 0.1 mol/L sodium phosphate buffer (pH 7.3). The temporal bones were immediately removed and stored overnight in cold fixative. After dissection, cochleas were decalcified in phosphate-buffered 10% ethylenediaminetetraacetic acid with 2% paraformaldehyde in saline at 2°C for 4 to 6 weeks, dehydrated in graded ethyl alcohols, embedded in Surgipath (Surgipath Medical Industries, Inc), and sectioned at 7 µm. Representative sections were mounted on clean slides and stained with hematoxylin and eosin for evaluation of inflammatory infiltrates. Adjacent sections were mounted on gelatin-coated slides and stained immunohistochemically[26] as follows. Deparaffinized sections were immersed for 20 minutes in 2% H_2O_2 in methanol to reduce endogenous peroxidases. After nonspecific antibody binding was blocked by incubation for 1 hour at 37°C with 20% normal guinea pig serum from seronegative animals, sections were washed three times in PBS. Antigen-specific labeling was then achieved by incubation for 24 hours at 4°C with biotinylated anti-GPCMV immunoglobulin (Ig) G from seropositive guinea pigs. After washing in PBS, streptavidin–horseradish peroxidase conjugate (BRL Life Tech, Gaithersburg, Md) was applied for 30 minutes at 37°C, followed by 10-minute incubation in the dark at 24°C with the chromogen 3-amino-9-ethylcarbazole plus 0.1% H_2O_2. Sections were then counterstained with hematoxylin. A negative control was established by using biotinylated seronegative guinea pig IgG on alternate sections in place of anti-GPCMV sera. Cultured GPCMV-infected and noninfected guinea pig embryo cells were also processed as above and placed on each slide as a control. Cells expressing GPCMV antigen were identified under the microscope by a reddish brown reaction product within the confines of the cellular membrane.

The relative inflammatory reaction in the inner ear of each animal inoculated with GPCMV was determined independently by two of the authors without knowledge of treatment group. The primary criteria for assigning rank order were the density and extent of the inflammatory infiltrate, fibromyxoid reaction, hemorrhage, and edema in the cochlea. Ranks assigned by the two investigators were averaged for each animal and plotted against the CAP threshold. The amount of GPCMV antigen within cells in the cochlea was assessed by drawing on a tracing of the guinea pig cochlea the location of reaction product. Comparison of the amount of GPCMV antigen in the cochlea was then made between tracings from cyclophosphamide-treated versus nonimmunosuppressed guinea pigs to determine if immunosuppression affected the amount of GPCMV infection.

Measurement of Immunosuppression. Blood samples drawn by cardiac puncture were taken from cyclophosphamide-immunosuppressed and saline-treated noninoculated animals on days 0, 2, 6, and 13 of treatment. Total leukocyte count was measured by a Coulter counter (Coulter S-Plus IV, Coulter Electronics, Hialeah, Fla), and leukocyte differential counts were determined from Wright's stained blood smears by counting 200 cells. The absolute number of lymphocytes and neutrophils was calculated by multiplying the total leukocyte count by the percentage of these cell populations.

Lymphocytes from GPCMV-inoculated and noninoculated animals were tested for their in vitro blastogenic responses. After 13 days of IP injections with cyclophosphamide or saline, 15 to 20 mL of peripheral blood was drawn by cardiac puncture. Mononuclear cells were harvested from peripheral blood as described previously.[35] Cervical lymph nodes and the spleen were removed aseptically and a section of spleen was taken for histologic examination. Suspensions of splenic and lymph node mononuclear cells were obtained by teasing the spleen or lymph nodes apart and passing the suspensions through a 60-mesh wire screen. The harvested cells from peripheral blood, lymph nodes, and spleen were then washed, pelleted, and resuspended in RPMI-1640 with 10% fetal bovine serum and 50 μg/mL gentamicin (culture medium). A 100-μL aliquot was mixed 1:1 with a 10% solution of trypan blue, and nucleated lymphocytes that excluded dye were counted on a hemocytometer. Suspensions were adjusted in culture medium to a density of 2×10^5 cells per 200 μL solution.

Quadruplicate wells, each containing 2×10^5 lymphocytes per 200 μL culture medium, were prepared in 96-well, flat-bottomed microtiter plates, stimulated with phytohemagglutinin (PHA), pulsed with [^{3}H]thymidine, and harvested as described previously.[35] Net incorporation of radiolabel by cells was expressed as the mean counts per minute in quadruplicate PHA-stimulated cultures minus the counts per minute in quadruplicate unstimulated cultures.

Experimental Design and Statistical Analysis. Two groups of guinea pigs were used in this study: GPCMV-inoculated and noninoculated. This was done so that the health of GPCMV-inoculated animals, from which CAP threshold data were obtained, was not compromised by repeated manipulation. Data on the effect of cyclophosphamide on the blastogenic response of lymphocytes to PHA were obtained from both GPCMV-inoculated and noninoculated guinea pigs because these measures could be obtained at the time of animal death. Treatment groups were 1) cyclophosphamide IP, GPCMV-inoculated (group 1A received live GPCMV in the right ear and group 1B received inactivated GPCMV in the left ear; n = 10), 2) cyclophosphamide IP, noninoculated (n = 10), 3) saline IP, GPCMV-inoculated (group 3A received live GPCMV in the right ear and group 3B received inactivated GPCMV in the left ear; n = 7), and 4) saline IP, noninoculated (n = 10). Mean blastogenic responses for a given lymphocyte source at a given concentration of PHA were submitted to analysis of variance (ANOVA). In each case, the lack of significant effect of GPCMV inoculation ($p > .05$) and lack of interaction between treatment and GPCMV inoculation allowed treatment main effects to be separated by ANOVA.

Only noninoculated animals were used to obtain data on total leukocyte count, lymphocyte count, and neutrophil count; data from five animals showed that peripheral blood indices in GPCMV-inoculated and noninoculated animals were affected by cyclophosphamide in a similar manner. Cell counts for each sampling time were obtained twice, with five cyclophosphamide-treated (group 2) and five nonimmunosuppressed guinea pigs (group 4) in each experiment. Data from the two experiments on the effect of cyclophosphamide on peripheral blood cell counts were analyzed by ANOVA, and means were then compared by Fisher's least significant difference (LSD) test.

The effect of immunosuppression on the CAP threshold in guinea pigs inoculated with GPCMV was tested twice, on days 0 and 7 after GPCMV inoculation in the following treatment subgroups: 1A) cyclophosphamide IP, live GPCMV inner ear inoculation (n = 10), 1B) cyclophosphamide IP, inactivated GPCMV inner ear inoculation (n = 10), 3A) saline IP, live GPCMV inner ear inoculation (n = 7), and 3B) saline IP, inactivated GPCMV inner ear inoculation (n = 7). Data on the effect of in-

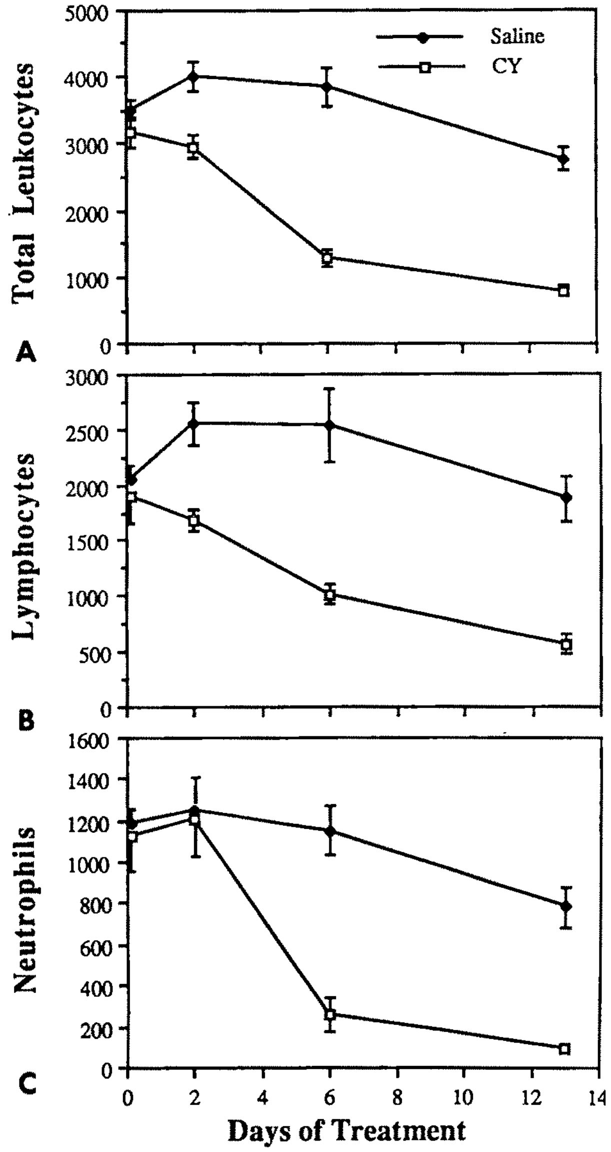

Fig 1. Effect of cyclophosphamide (CY) on A) total leukocytes, B) lymphocytes, and C) neutrophils per cubic millimeter of peripheral blood from uninfected guinea pigs. Values represent mean ± SE. Total leukocytes, lymphocytes, and neutrophils were significantly depleted in CY-treated animals (group 2 animals) compared to saline-treated controls (group 4 animals) by 6 days of immunosuppression ($p<.01$, Fisher's least significant difference). Number of these peripheral blood cells was constant in saline-treated animals until day 6. Between days 6 and 13, total leukocytes, but not lymphocytes or neutrophils, decreased significantly ($p<.01$, Fisher's least significant difference).

activated virus on hearing (groups 1 and 3), which served as a control for the invasive procedures involved in inner ear inoculation, were subjected to ANOVA. Means for the combined data were compared by Fisher's LSD. Data on the effect of live GPCMV on hearing were analyzed in the same manner.

RESULTS

Assessment of Immunosuppression. There was no difference in the overall appearance of guinea pigs treated with cyclophosphamide compared to those treated with saline.

Total peripheral blood leukocytes (Fig 1A), lymphocytes (Fig 1B), and neutrophils (Fig 1C) were depleted in cyclophosphamide-treated guinea pigs compared to saline-treated animals by day 6 of treatment ($p<.01$, Fisher's LSD). After 13 days of cyclophosphamide treatment, only 25% of the original number of circulating leukocytes remained. Cyclophosphamide treatment depleted neutrophils more than lymphocytes; lymphocytes were reduced to 30% of their initial value, while only 8% of the initial number of neutrophils remained after 13 days of immunosuppression. The number of peripheral blood leukocytes was constant in saline-treated guinea pigs until day 6, but decreased significantly between days 6 and 13 (Fig 1A) ($p<.01$, Fisher's LSD). This late decrease in leukocytes was accompanied by a downward but insignificant trend in the number of lymphocytes (Fig 1B) and neutrophils (Fig 1C). Hemodilution from repeated blood sampling may have contributed to the leukopenia on day 13.

Lymphocytes isolated from the peripheral blood and the spleen of cyclophosphamide-treated guinea pigs incorporated a significantly lower amount of [^{3}H]thymidine in response to stimulation with 1.0 μg/mL PHA than peripheral blood ($p = .004$) and splenic lymphocytes ($p = .003$) from saline-treated animals (see Table). Splenic lymphocytes from cyclophosphamide-treated guinea pigs also responded less to 0.5 μg/mL PHA than lymphocytes from the spleen of saline-treated controls ($p = .014$). However, treatment with cyclophosphamide did not affect the PHA-stimulated net incorporation of [^{3}H]thymidine in cervical lymph node lymphocytes.

Eighth Nerve Compound Action Potential Threshold. The eighth nerve CAP threshold was unchanged before and 7 days after inoculation of inactivated GPCMV into the scala tympani of either cyclophosphamide- or saline-treated guinea pigs (Fig 2). These data were gathered as a control for the surgical technique, fluid injection, and auditory nerve recordings, and indicated that these invasive procedures did not impair hearing.

Inoculation of GPCMV into the scala tympani of saline-treated guinea pigs produced a significant increase in the CAP threshold 7 days after inoculation compared to the baseline measurement on the day of inoculation (Fig 2) ($p<.01$, Fisher's LSD). Inoculation of GPCMV into cyclophosphamide-treated animals, however, resulted in less hearing loss. The CAP threshold on day 7 after GPCMV inoculation was an average of 35 dB less for cyclophosphamide-treated compared to saline-treated guinea pigs ($p<.01$, Fisher's LSD). Further, the CAP threshold for 6 of the 10 immunosuppressed guinea pigs was more

GUINEA PIG LYMPHOCYTE BLASTOGENIC RESPONSE TO PHA

	Lymphocyte Source				
	Peripheral Blood	*Spleen*		*Cervical Lymph Nodes*	
	1.0 μg/mL PHA	*0.5 μg/mL PHA*	*1.0 μg/mL PHA*	*0.5 μg/mL PHA*	*1.0 μg/mL PHA*
Cyclophosphamide*	4,350± 1,739†	2,270± 651§	2,507± 688§	3,460±1,462	4,636±1,190
GPCMV-positive	3,112± 2,240	1,445± 610	1,867± 782	1,869± 802	2,954± 906
GPCMV-negative	5,340± 2,630	3,096±1,125	3,147±1,139	5,050±2,797	6,318±2,127
Saline	27,909± 7,889	11,631±3,728	14,160±3,811	3,309±1,929	3,780±1,201
GPCMV-positive	11,450± 9,877	7,427±3,802	8,380±3,445	2,441±1,063	4,059±1,088
GPCMV-negative	36,138±10,048	13,734±5,266	17,050±5,335	3,792±3,002	3,625±1,819

Values are mean±SE [^{3}H]thymidine incorporation in quadruplicate PHA-stimulated cultures minus that in unstimulated cultures.

PHA — phytohemagglutinin, GPCMV — guinea pig cytomegalovirus.

*Cyclophosphamide (20 mg/kg body weight) and equal volume of phosphate-buffered saline were given daily for 13 days by intraperitoneal injection.

†Significantly lower than peripheral blood lymphocytes from saline controls (p<.01).

§Significantly lower than splenic lymphocytes from saline controls (p<.01).

than 2 SD below the mean for saline-treated controls.

Cochlear Histopathology. Guinea pigs inoculated with live GPCMV in the scala tympani showed no difference in the amount or the distribution of GPCMV antigen within the cochlea whether they were treated systemically with cyclophosphamide or with saline. Control sections incubated with IgG from seronegative animals and those from cochleas inoculated with inactivated GPCMV contained no labeled cells.

Guinea pig CMV antigen was consistently found in tympanic lamellar cells below the basilar membrane, mesothelial cells lining the scala tympani, and inflammatory cells within the perilymphatic duct of the basal turn of the scala tympani. Less frequently, inflammatory cells within the osseous spiral lamina, Rosenthal's canal, and the spiral ligament expressed GPCMV antigen. The tympanic lamellar cells were presumably more susceptible to infection than any other cell in the cochlea.[26] Infection was sparse in the scala tympani of the apical turns and did not spread into the scala media or the organ of Corti.

The inflammatory infiltrate in the cochlea 7 days after inoculation of live GPCMV into the scala tympani consisted of many neutrophils; fewer lymphocytes, plasma cells, and macrophages; and occasional giant cells throughout the scala tympani of the basal turn of the cochlea (Fig 3A). This infiltrate extended into but was decreased in density in the spiral ligament, osseous spiral lamina, and scala vestibuli. A fibromyxoid reaction was most prominent in the scala tympani of the basal turn, but also formed to a lesser degree in the scala media and extended toward the apex. Hemorrhage was apparent throughout all turns and within the spiral ligament, stria vascularis, and Rosenthal's canal. The stria vascularis was edematous and showed signs of degeneration. Reissner's membrane was intact and hydrops was not present. These inflammatory changes were decreased in cyclophosphamide-treated animals such that in some the only pathologic finding in the cochlea was a sparse inflammatory infiltrate confined to the scala tympani of the basal turn, without fibromyxoid reaction, hemorrhage, or edema (Fig 3B). Inoculation of inactivated GPCMV into the scala tympani produced no histopathologic changes in the cochlea.

The relative amount of GPCMV antigen in the cochlea did not correlate with immunosuppression or with the CAP threshold. On the other hand, animals with the less extensive inflammatory response in the cochlea had a lower CAP threshold and thus the greatest preservation of hearing (Fig 4). Also, less extensive cochlear histopathology occurred in cyclophosphamide-immunosuppressed animals than in those treated with saline.

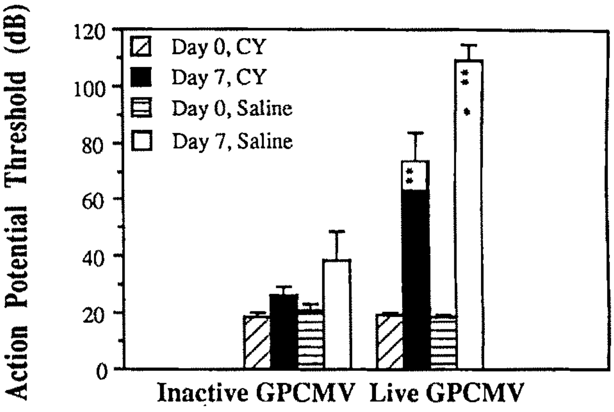

Fig 2. Effect of cyclophosphamide (CY) on eighth nerve compound action potential threshold (dB sound pressure level) of guinea pigs on day 0 (before inoculation of guinea pig cytomegalovirus [GPCMV]) and day 7 after inoculation of live or inactivated GPCMV into scala tympani. Live GPCMV was placed in right scala tympani, and psoralen- and ultraviolet light–inactivated GPCMV was inoculated into left scala tympani of each animal. Guinea pigs were pretreated with CY or saline for 6 days before GPCMV inoculation and continued to receive these treatments for 7 days after virus inoculation. Values represent mean±SE. Animals were from following treatment groups: 1A) CY, live GPCMV inoculated into right scala tympani, 1B) CY, inactivated GPCMV inoculated into left scala tympani, 3A) saline, live GPCMV, and 3B) saline, inactivated GPCMV. * — p<.01 compared to respective day 0 value, ** — p<.01 compared to day 7, CY.

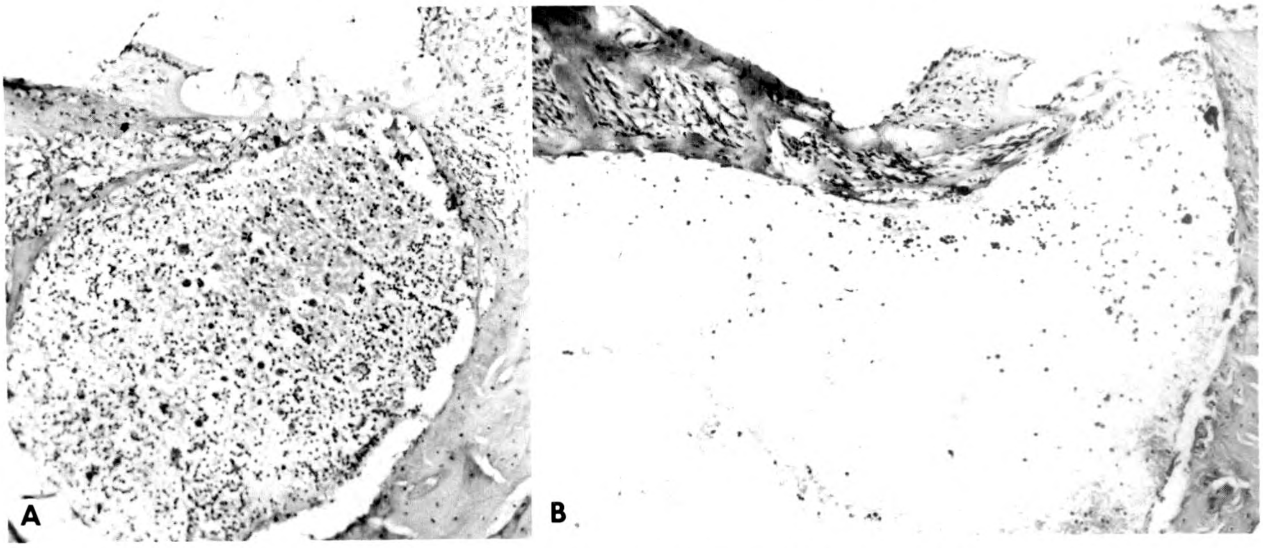

Fig 3. Micrograph showing inflammatory infiltrate in basal turn of guinea pig cochlea 7 days after inoculation of live guinea pig cytomegalovirus (GPCMV) into scala tympani of seronegative A) immune-competent guinea pig, and B) guinea pig immunosuppressed with cyclophosphamide (20 mg/kg body weight). Immunosuppression led to markedly decreased inflammatory reaction to infection with GPCMV, including less fibromyxoid reaction, hemorrhage, or edema and fewer infiltrating neutrophils, plasma cells, or macrophages.

DISCUSSION

The indices of immunosuppression used in this study indicate that the administration of cyclophosphamide (20 mg/kg body weight) for 6 days before inoculation of GPCMV into the inner ear assured that the immune system was suppressed throughout the time that inner ear structures were exposed to GPCMV. Blastogenic responses of lymphocytes from peripheral blood and the spleen were decreased in cyclophosphamide-treated animals, suggestive of a compromised ability to respond to an inciting antigen. However, lymphocytes from cervical lymph nodes of cyclophosphamide- and saline-treated guinea pigs responded similarly to PHA; this finding suggests that their function was not affected by cyclophosphamide treatment. Conflicting results have been reported on the blastogenic response to PHA of lymphocytes from guinea pigs. Winkelstein[30] found that treatment with cyclophosphamide (20 mg/kg body weight for 7 days) significantly impaired the in vitro proliferative response of lymph node lymphocytes to PHA, while Balow et al[32] found that the proliferative response of peripheral blood lymphocytes from guinea pigs treated with cyclophosphamide (20 mg/kg body weight for 5 days) was decreased only in response to 0.5 μg/mL PHA and not 1.0 μg/mL PHA. Balow et al concluded that the mitogenic response of peripheral blood lymphocytes remaining in the circulation after cyclophosphamide immunosuppression was relatively well preserved.

This study clearly implicates the immune response to GPCMV in the cochlea as a causative factor in the hearing loss of GPCMV labyrinthitis. When the pathologic changes associated with viral infection are reduced by immunosuppression, it is generally assumed that the inflammatory reaction contributed to the pathogenesis of the disease.[36] In this study, immunosuppression with cyclophosphamide resulted in a significant preservation of hearing, as control animals, on the average, were deaf, while cyclophosphamide-treated animals had only a moderate hearing impairment. Furthermore, approximately two thirds of the immunosuppressed animals had functionally intact hearing, with a CAP threshold more than 2 SD below that of control animals. A positive correlation was found between the degree and extent of the inflammatory reaction in the cochlea and hearing loss; such a relationship was not found for the level of GPCMV antigen in the cochlea. This suggests that the immune response may be even more important than direct

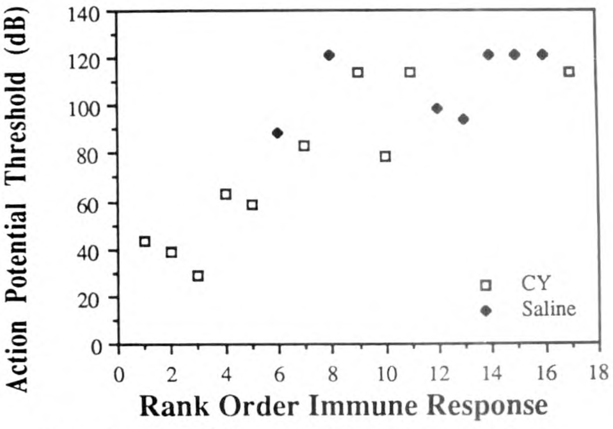

Fig 4. Correlation between eighth nerve compound action potential threshold and degree and extent of immune response in cochlea for cyclophosphamide (CY)– and saline-treated guinea pigs 7 days after inoculation of guinea pig cytomegalovirus into scala tympani. Numbers on x-axis indicate rank order of animals from 1 (least amount of immune response) to 17 (most).

cytopathic effects of the virus in producing hearing loss.

Also of note, immunosuppression with a daily cyclophosphamide dose of 20 mg/kg body weight did not result in an unleashing of viral infection. Often, adequate immunosuppression potentiates sublethal viral infections and produces persistent viral replication and increased numbers of infected and destroyed cells in target organs.[37] In this study, there was no apparent difference in the amount of GPCMV infection in the cochlea of cyclophosphamide-treated guinea pigs compared to controls after 7 days of infection. Systemic spread of GPCMV from the inner ear did not occur either, as evidenced by the lack of GPCMV infection in the contralateral ear and the spleen.

The mechanism of hearing loss in acute GPCMV labyrinthitis is not known. Humoral immunity does not seem to be primarily involved, however, because inoculation of live GPCMV into the scala tympani of seronegative guinea pigs leads inexorably to deafness before the appearance of perilymphatic[23] or serum[27] antibody to GPCMV. Cell-mediated immunity is the principal arm of the acute immune response to CMV infection[38]; suppression of the cellular immune response by cyclophosphamide was presumably responsible for the preservation of hearing in the guinea pigs with GPCMV labyrinthitis. Cytomegalovirus-induced injury during chronic infection in the human is postulated to involve persistent low-grade viral replication in affected organs, reactivation of latent virus, vasculitis,[39] and/or immune complex formation,[40] and may occur as a result of a CMV-specific defect in cell-mediated immunity.[41] More specific modulation of the various arms of the immune system may help to further dissect out the component(s) of the immune response that are most directly associated with CMV-induced hearing loss. Quantitation of immunoglobulins and inflammatory cell subclasses in the cochlea, and a search for inner ear immune complex deposits during chronic GPCMV labyrinthitis may also aid our understanding of the pathogenesis of hearing loss in human CMV labyrinthitis.

The inner ear has an immune system[42-45] that is capable of inducing focal injury, including SNHL,[44,45] to the cochlea. The endolymphatic sac, the primary site of inner ear immune responses, induces an inflammatory infiltrate in the cochlea in response to inner ear antigen challenge.[46,47] The inflammatory cells in the inner ear seem to be recruited from the systemic circulation via modiolar blood vessels.[48] Alternatively, the inflammatory infiltrate could stem partly from the expansion of a resident population of immune-competent cells in the endolymphatic sac.[49] Cyclophosphamide readily crosses the blood-brain barrier and presumably the blood-labyrinth barrier, and could exert its immunosuppressive effects on either population of immune cells.

Cyclophosphamide inhibits established immune responses[30,32] and is recommended for the treatment of certain cases of SNHL in a variety of disorders associated with altered immune reactivity.[50] In this study, some benefit was obtained from using cyclophosphamide to treat SNHL in GPCMV labyrinthitis. Combination treatment with cyclophosphamide and an anti-inflammatory agent such as prednisone is often efficacious in patients with recalcitrant autoimmune reactivity and may be appropriate in cases of SNHL of viral origin. Alternatively, the antiviral agent ganciclovir has prevented the development of cochlear histopathologic changes and hearing loss in GPCMV labyrinthitis.[51] Use of an antiviral agent such as ganciclovir could stabilize or reverse CMV-induced hearing loss and may be useful in combination with an immunosuppressive agent for the treatment of CMV-induced SNHL.

A recent study has also shown the beneficial effects on hearing preservation of dexamethasone, a known immunosuppressive agent, when added to antibiotics for the treatment of bacterial meningitis.[52] Thus, it seems that when pathogens provoke a vigorous inflammatory response within the inner ear, it is not well tolerated, and any methods by which this response can be ameliorated will improve the chance of hearing preservation.

ACKNOWLEDGMENTS — We thank Dr Stephen Baird for his assistance in evaluating spleen sections, and Drs Joshua Fierer and Douglas Richman for their helpful comments on the experimental design of this study.

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Ann Otol Rhinol Laryngol 99:1990

IDIOPATHIC SUDDEN SENSORINEURAL HEARING LOSS AND POSTNATAL VIRAL LABYRINTHITIS: A STATISTICAL COMPARISON OF TEMPORAL BONE FINDINGS

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Although the cause of idiopathic sudden sensorineural hearing loss remains uncertain, a viral origin has been suggested in many cases on the basis of anamnestic microbiologic and pathologic data. Twenty-two temporal bone specimens from 18 patients who during life suffered a sudden partial or complete sensorineural hearing loss were studied. On the basis of clinical data, these cases were assigned to one of three diagnostic categories, and the temporal bones were studied by light microscopy and serial section analysis. The implications of the histopathologic findings for the pathogenesis of idiopathic sudden sensorineural hearing loss are discussed.

KEY WORDS — idiopathic sudden sensorineural hearing loss, postnatal viral labyrinthitis, temporal bone.

INTRODUCTION

As in 1944, when it was first described,[1] idiopathic sudden sensorineural hearing loss (ISSHL) remains an etiologic and therapeutic enigma. Historical and anamnestic data, as well as microbiologic and pathologic findings, have been cited in support of a viral cause of ISSHL. Clinically, in 25% to 33% of all cases of ISSHL there is a history of a preceding or concurrent upper respiratory tract infection.[2-5] Elevation of antibody titers to several viral agents has been demonstrated in patients with ISSHL.[2,5-12] Temporal bone histopathology in ISSHL has been described as similar to that of "known" postnatal viral labyrinthitis, eg, mumps and measles.[13-18] In animal models produced after injection of viruses into the brain, peritoneum, and labyrinth, viral antigens have been found in different parts of the inner ear.[19-25] Although this finding has been cited in support of a viral labyrinthitis, neither hearing thresholds nor action potentials were tested in these animals. Consequently, these experiments may simply reflect a local or systemic dissemination of the virus to multiple organs, including the ear. Abnormal cochlear morphology and a progressive (not sudden) hearing loss have been documented in experimental cytomegaloviral labyrinthitis in the guinea pig.[26,27] Therefore, to date no animal model for viral labyrinthitis with sudden hearing loss has been described.

Although none of these data are conclusive, they show a possible association between viruses and some cases of ISSHL. On the other hand, a previous report from this laboratory[28] documented a significant difference in counts of remaining spiral ganglion cells in temporal bones from patients with ISSHL as compared to cases of postnatal viral labyrinthitis. This study provided the impetus for our present work. A quantitative analysis of cochlear and neuronal elements in temporal bones of patients with ISSHL and postnatal viral labyrinthitis was performed to assess the histologic parameters in these clinical entities.

MATERIALS AND METHODS

In the human temporal bone collection at the Massachusetts Eye and Ear Infirmary there are 22 specimens from 18 patients who during life had documented sudden partial or complete hearing loss. On the basis of clinical data, these cases were assigned to one of three diagnostic categories.

Group 1: ISSHL with no history of an upper respiratory tract infection (seven ears; six patients, including one with bilateral sequential hearing loss).
Group 2: ISSHL with a history of upper respiratory tract infection preceding or occurring concurrently with the hearing loss (six ears; six patients).
Group 3: postnatal presumptive viral labyrinthitis, consisting of cases of profound hearing loss in one or both ears following an attack of measles, mumps, or herpes zoster oticus (nine ears; six patients).

Thus, the clinical evidence for a viral cause was the strongest in group 3 and absent in group 1. None of the patients had viral antibody titer or isolation tests at the time of hearing loss.

All temporal bones were fixed in Heidenhain Susa solution, decalcified in trichloroacetic acid, and

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Presented at the meeting of the American Otological Society, Inc, Palm Beach, Florida, April 28-29, 1990.

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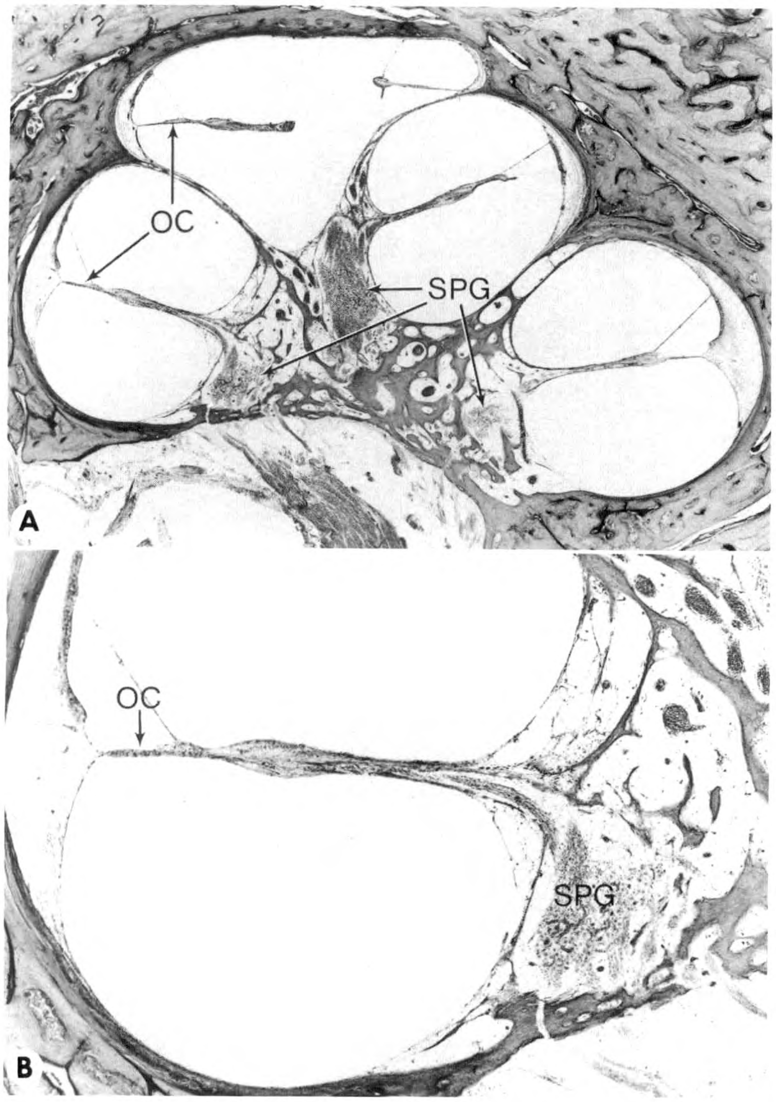

Fig 1. (Case 1) Temporal bone histopathologic findings in individual with idiopathic sudden sensorineural hearing loss 6 years prior to death with no history of viral infection (group 1). OC — organ of Corti, SPG — spiral ganglion cells. A) Midmodiolar section demonstrating that major histopathologic correlate of this profound deafness was degeneration of OC (H & E, original x29). Spiral ganglion cell population was normal in middle and apical turns and moderately reduced in basal turn. B) Higher-power micrograph of basal turn demonstrating loss of OC and preservation of large number of SPG (H & E, original x79).

embedded in celloidin.[29] The temporal bones were sectioned at a thickness of 20 μm in the horizontal plane. Every 10th section was stained with hematoxylin and eosin and mounted on a glass slide. All temporal bones were studied in a single blind random fashion. The patient's name on each slide of the temporal bone was masked. The open slide trays were then randomly intermixed and separately analyzed. At the end of the analysis the names were revealed and matched with their respective reconstruction.

The organ of Corti was graphically reconstructed by the method described by Schuknecht.[29] Each of the structures of the cochlear duct (hair cells, pillar cells, spiral limbus cellularity, stria vascularis, and tectorial membrane) was assessed at approximately 100 loci in each temporal bone. The criteria for normality at each locus included the demonstration of one inner hair cell, three outer hair cells, an inner and an outer pillar cell with rods, stria vascularis with all three layers extending from the vestibular crest to the slope of the spiral prominence, and the presence of inner sulcus cells, fibrocytes, and interdental cells in the spiral limbus. Pathologic findings were quantified as a percentage of normal. Thus, for the tectorial membrane, a rolled-up or encapsulated membrane or a markedly atrophic membrane displaced into the inner sulcus region or embedded in the organ of Corti was considered grossly abnormal and assigned a score of 0%. For hair and pillar cells, the number of cells present compared to expected was expressed as a percentage of normal. The percentage of strial loss and cellularity of the spiral limbus was estimated in increments of 10%. The percentage loss for each structure was then averaged over all 100 loci to achieve a volumetric estimate of cochlear pathologic findings.

Spiral ganglion cells were counted by the technique described by Otte et al.[30] In cases of unilateral sudden deafness (eight ears: three in group 1, three in group 2, two in group 3), spiral ganglion cell counts were performed on the opposite ear to obtain an intrasubject control, allowing an estimate of the loss of spiral ganglion cells from aging and

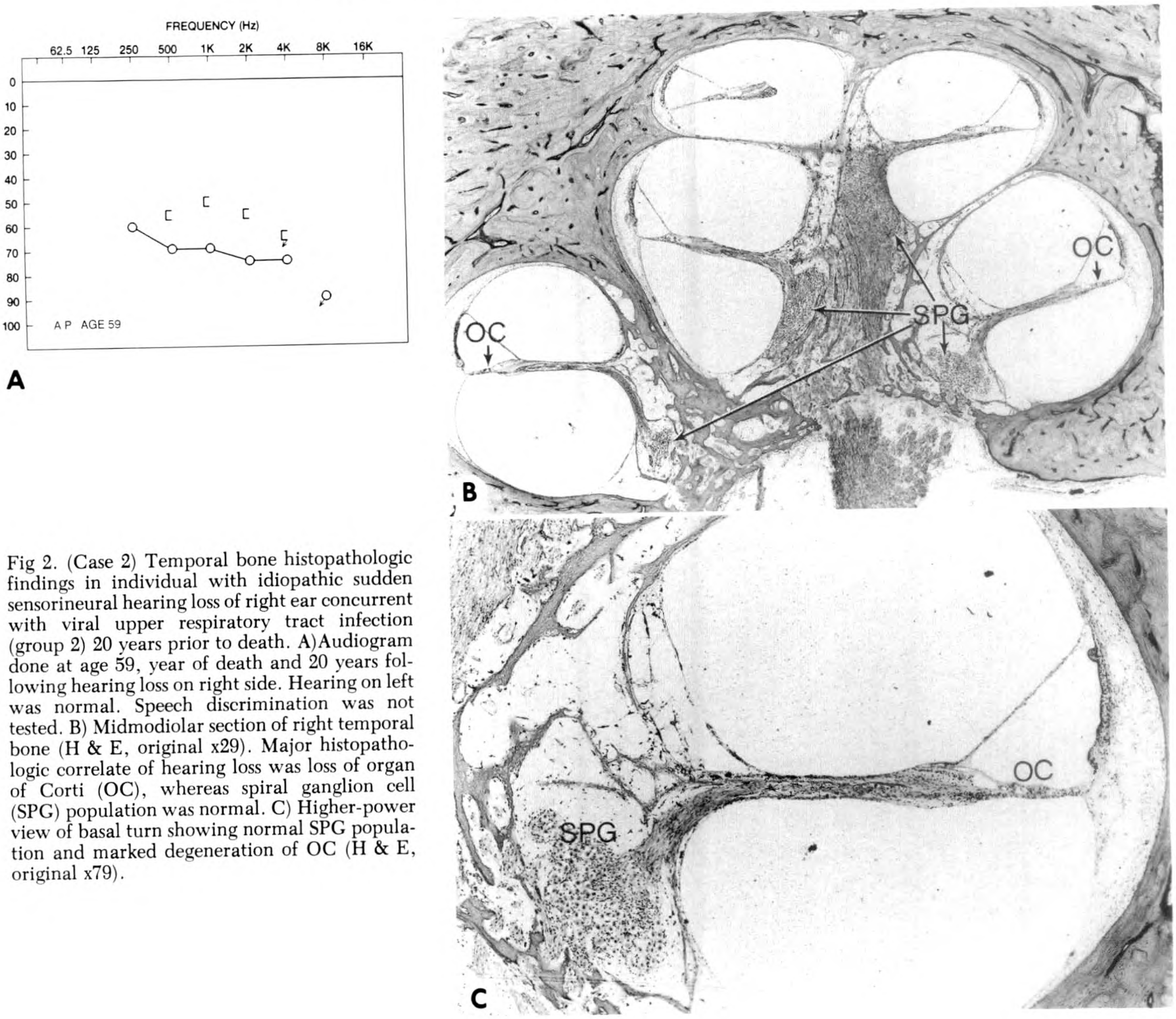

Fig 2. (Case 2) Temporal bone histopathologic findings in individual with idiopathic sudden sensorineural hearing loss of right ear concurrent with viral upper respiratory tract infection (group 2) 20 years prior to death. A) Audiogram done at age 59, year of death and 20 years following hearing loss on right side. Hearing on left was normal. Speech discrimination was not tested. B) Midmodiolar section of right temporal bone (H & E, original x29). Major histopathologic correlate of hearing loss was loss of organ of Corti (OC), whereas spiral ganglion cell (SPG) population was normal. C) Higher-power view of basal turn showing normal SPG population and marked degeneration of OC (H & E, original x79).

genetic factors. The difference between the initial count and a recount of the spiral ganglion cells was less than 10%.

Statistical analysis of the data obtained from the three diagnostic groups, each comprising six ears, was then performed with BMDP statistical software.[31] Analysis of variance and *t* tests were used to determine statistical significance. The Bonferroni approach was used to assess statistical significance for multiple comparisons. Pearson correlation coefficients between pairs of variables were calculated for each diagnostic group. The coefficient value was then compared to a 5% confidence level value on a standard two-tailed significance level chart.[32] The applicable degrees of freedom were obtained from the formula $df = n - 2$, where n is the number of cases in each group. In all groups the *df* value was 4.

CASE REPORTS

Case 1 (Group 1). At the age of 65 this man experienced a sudden profound sensorineural hearing loss in his left ear that persisted until the time of his death 6 years later. This was associated with nausea and vomiting that lasted for several hours. There was no history of an upper respiratory tract infection or other illness. Histologic study revealed atrophic changes in the organ of Corti with loss of pillar and hair cells. There was a total loss of the organ of Corti in the basal 15 mm. There was moderately severe atrophy of the stria vascularis at various locations in the cochlea and partial loss of ganglion cells in the basal turn (Fig 1). The vestibular labyrinth was normal.

Case 2 (Group 2). At the age of 39 this patient awakened with hearing loss and tinnitus in the right ear. She had complained of a concurrent head cold and nasal stuffiness. There was no history of vertigo. At the age of 59, the year of her death, audiometric tests showed a moderate sensorineural hearing loss (Fig 2A) on the right and normal hearing on the left. Tests of speech discrimination were not

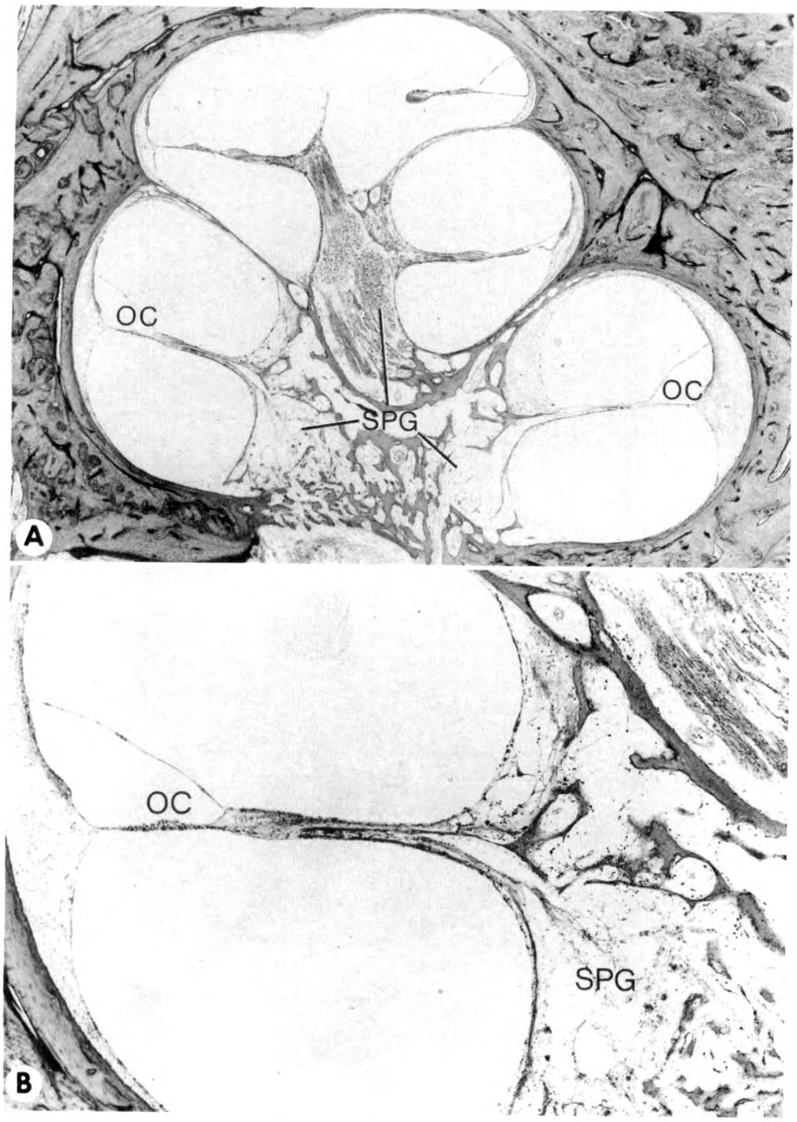

Fig 3. (Case 3) Temporal bone histopathologic findings in individual who became profoundly deaf at age of 4 years following illness diagnosed as measles (group 3). She died at age 53 years. OC — organ of Corti, SPG — spiral ganglion cells. A) Midmodiolar section of left temporal bone (H & E, original x29). There was total loss of hair cells in OC and moderate to severe loss of SPG, particularly in basal turn. B) Higher-power view of OC of basal turn demonstrating total loss of neural epithelial cells of OC and severe loss of SPG (H & E, original x79).

done. Histologic studies revealed a moderate loss of hair cells of the cochlea and a severe loss of hair cells in the saccule of the right ear. The spiral ganglion cell population was normal (Fig 2B,C). The organ of Corti, cochlear neurons, vestibular sense organs, and neurons of the left ear appeared normal.

Case 3 (Group 3). This patient is known to have been profoundly deaf following an illness diagnosed as measles at the age of 4 years. She died at age 53 of acute myocardial infarction. Histologic study showed severe loss of hair cells on the right and total loss on the left. There was a severe loss of stria vascularis bilaterally and a severe endolymphatic hydrops in the right ear. A moderately severe loss of spiral ganglion cells was seen bilaterally that was maximal at the base (Fig 3). The saccular maculae showed patchy atrophy bilaterally, but it was more severe on the right. The utricular macula was normal on the left and showed mild atrophy on the right.

RESULTS

The results of the analyses were based on one ear chosen at random from each donor. The parametric findings in each of groups 1, 2, and 3 are presented in Table 1. In groups 1 and 3, all ears tabulated were deaf to the limits of clinical audiometry. However, three cases of partial hearing loss were included in group 2. Four individuals (one from group 1 and three from group 3) had bilateral cochlear involvement. Because the right and left ear findings in the same individual may be similar and nonrandom, only one ear from each of these individuals was chosen at random to enhance the validity of the data. The mean and SD of measured parameters for each group are shown in Table 2. Nominal p values for variance *t* tests between pairs of diagnostic groups are shown in Table 3. The Bonferroni approach was used to assess statistical significance.

Statistically significant differences between groups 1 and 2 were found only in the loss of inner and outer hair cells and pillar cells.

Between groups 1 and 3, statistically significant

TABLE 1. QUANTITATIVE COCHLEAR AND NEURONAL FINDINGS

Case	*Loss of Spiral Limbus Cellularity (%)*	*Abnormality of Tectorial Membrane (%)*	*Pillar Cell Loss (%)*	*Hair Cell Loss (%)*		*Atrophy of Stria Vascularis (%)*	*Spiral Ganglion Cell Counts*	
				Inner	*Outer*		*Pathologic Ear*	*Normal Ear*
Group 1								
1	1	65	100	100	100	7	16,778	—
2	1	14	60	90	96	40	25,107	25,361
3	52	20	87	87	94	76	10,251	—
4	1	1	72	96	97	4	23,661	26,496
5	11	67	86	67	75	8	14,135	—
6	5	95	98	96	89	4	20,871	19,872
Group 2								
1	14	90	95	85	90	56	6,003	—
2	3	10	25	35	50	1	31,014	27,019
3	0	0	26	38	41	16	22,917	21,141
4	3	100	5	10	10	10	26,568	—
5	0	5	10	22	15	24	20,178	22,716
6	0	4	10	4	4	6	0	—
Group 3								
1	20	10	94	94	93	79	4,473	—
2	5	40	100	100	100	11	2,457	—
3	2	76	100	100	100	6	801	—
4	35	75	100	98	99	68	7,929	—
5	98	60	100	100	100	100	0	28,833
6	42	85	97	95	97	40	17,595	22,455

Dash — no data available.

differences were found in age at hearing loss and in counts of remaining ganglion cells. For the pairs of diagnostic groups 2 and 3, statistically significant differences were found in age at hearing loss, loss of pillar cells, and loss of inner and outer hair cells. Across the three groups, differences in age at death, sex, test autopsy interval, and contralateral ganglion cell counts were not significant.

Thus, on the basis of morphologic parameters, the spiral ganglion cell count was significantly lower in group 3 (presumptive viral-associated sensorineural deafness) than in group 1 and the hair cell and pillar cell losses were significantly greater in groups 1 and 3 than in group 2.

For structures within the cochlear duct (hair cells, pillar cells, stria vascularis, tectorial membrane, and limbus), the most remarkable differences were between groups 2 and 3. However, there was great pathologic (Table 1) and audiometric heterogeneity among the six ears in group 2. Thus, in one case there was an isolated tectorial membrane abnormality (case 4), whereas in another (case 6) there was an isolated cochlear neuropathy with severe ganglion cell loss. Both these ears show a nearly normal complement of hair and pillar cells. Besides these two pathologic outliers, three patients in group 2 (cases 2, 3, and 5) had moderate hearing losses (pure tone averages for speech frequencies, 57.5 to 67.5 dB), while the remaining three had profound losses.

Wherever possible, the spiral ganglion cells in the opposite unaffected ears (ie, three ears in group 1, three in group 2, two in group 3) were counted. Except for the two ears in group 3, the differences in total ganglion cell counts between "unaffected" and "affected" ears of the same donor were small (Table 1); this finding suggests that the decreases in neuronal counts in pathologic ears of groups 1 and 2 were due to other factors such as aging and not to the etiologic mechanism that resulted in sudden loss of hearing. However, the spiral ganglion counts in the deafened ears of group 3 were markedly reduced from normal for age and from the contralateral ear (Table 2); this finding suggests that neuronal involvement was inherent to the mechanism of deafness in this group.

Pearson correlation coefficients were calculated to test the strength of associations between various variables within each group. Although the associations varied from weak to moderately strong, very few reached statistically significant levels. These are shown in Table 4. Across the three groups, the remaining ganglion cell count did not consistently correlate with any variable, including the duration of hearing loss or degeneration of inner hair cells. In all three groups there was a moderately strong correlation between pillar cell loss, inner and outer hair cell loss, and strial atrophy. This possibly reflects simultaneous involvement of all these structures at the time of injury. The patient's sex, age at onset of hearing loss, or the age at death did not correlate well with any variable.

DISCUSSION

The cause of idiopathic sudden sensorineural

TABLE 2. MEANS AND STANDARD DEVIATIONS OF VARIABLES IN THREE DIAGNOSTIC GROUPS

	Group 1		*Group 2*		*Group 3*	
	Mean	*SD*	*Mean*	*SD*	*Mean*	*SD*
Age at death (y)	63.7	14.4	59.7	16.5	49.0	24.3
Age at hearing loss (y)	52.0	15.8	48.5	18.7	13.2	24.3
Duration of hearing loss (y)	11.7	12.8	11.2	10.6	34.0	27.9
Sex (F = 1, M = 0)	0.3	0.5	0.3	0.5	0.2	0.4
Test autopsy interval (y)	7.5	6.8	4.2	7.4	4.9	8.1
Spiral limbus acellularity (%)	11.8	20.1	3.3	5.4	33.7	35.3
Tectorial membrane abnormality (%)	43.7	37.1	34.8	46.8	57.7	28.2
Pillar cell loss (%)	83.8	15.4	28.5	33.7	98.5	2.5
Inner hair cell loss (%)	89.3	11.9	32.3	29.1	97.8	2.7
Outer hair cell loss (%)	91.8	9.0	35.0	32.5	98.2	2.8
Strial atrophy (%)	23.2	24.3	18.8	19.9	50.7	38.0
Spiral ganglion cell count in diseased ear	18,467	5,761	17,780	12,160	5,543	6,555
Spiral ganglion cell count in unaffected ear	23,910	3,543	23,625	3,043	25,644	4,510

hearing loss remains speculative. More than 90% of the cases of ISSHL are unilateral.[3] In approximately 30% of cases there is a history of upper respiratory tract infection. Between 30% and 70% of patients have partial to complete recovery of function. The three most commonly cited theories of causation of ISSHL include viral infection,[6-10,18] vascular phenomena,[5,33,34] and intralabyrinthine membrane ruptures.[35] Of the three, the viral theory has accrued the most circumstantial evidence.

The incidence of positive serologic conversions from paired assays (acute and convalescent sera) has varied from 0% to 67%.[2,7-12] These studies have implicated mumps, influenza, parainfluenza, and adenovirus 3 as the commonest viral agents. In one case, mumps virus was isolated from the perilymph of a 26-year-old woman who presented with profound sudden sensorineural hearing loss following a mumps parotitis.[36] Studies of Veltri et al[7] and Wilson et al[10] have suggested that multiple viruses may be involved, perhaps by means of reactivation of latent viruses by acute infection with another viral strain. Clinical and histopathologic observations have implicated respiratory viruses as well as those of mumps, measles, rubella, and herpes zoster.

The purpose of this study was to critically reexamine and compare the histologic findings in the temporal bones of patients with ISSHL and presumptive postnatal viral labyrinthitis. The results of this parametric analysis demonstrated that the residual spiral ganglion cell count was lower ($p < .05$) in group 3 (viral labyrinthitis) than in group 1 (ISSHL) and the numbers of residual hair and pillar cells were greater in group 2 than in either group 1 or group 3. The mean spiral ganglion cell counts of groups 1 and 2 were 18,467 and 17,780, respectively, while that of group 3 was 5,543 (Table 2). Further, the spiral ganglion cell counts in the affected ears of groups 1 and 2 were similar to the counts in the opposite, "unaffected" ears, suggesting that spiral ganglion cell loss was not inherent to the pathogenesis of the ISSHL. In marked contrast, the mean

TABLE 3. NOMINAL P VALUES FOR SEPARATE VARIANCE *T* TEST BETWEEN PAIRS OF DIAGNOSTIC GROUPS

	1 vs 2	*1 vs 3*	*2 vs 3*
Age at death	.6650	.2392	.3978
Age at hearing loss	.7334	.0087* (.0037*)	.170 (.0069*)
Duration of hearing loss	.9446	.1032	.0932
Sex	1.0000	.5498	.5498
Test autopsy interval	.4370	.6124	.8954
Spiral limbus acellularity	.3571	.2244	.0896 (.0420)
Tectorial membrane abnormality	.7252	.4801	.3354
Pillar cell loss	.0081* (.0004†)	.0672	.0038* (.0000§)
Inner hair cell loss	.0035* (.0001§)	.1435	.0026† (.0000§)
Outer hair cell loss	.0068* (.0001§)	.1520	.0050* (.0001§)
Strial atrophy	.7715	.1928	.1090
Spiral ganglion cell count in diseased ear	.9039	.0048*	.0634
Spiral ganglion cell count in unaffected ear	.9212	.6977	.6510

Numbers in parentheses are pooled variance p values.

*$p < .05$.

†$p < .01$.

§$p < .001$.

TABLE 4. PEARSON CORRELATION COEFFICIENTS FOR PAIRS OF VARIABLES

	Duration of Hearing Loss	*Inner Hair Cell Loss*	*Pillar Cell Loss*	*Outer Hair Cell Loss*	*Strial Atrophy*
Group 1					
Inner hair cell loss	−.62				
Pillar cell loss	.09	−.13			
Outer hair cell loss	−.38	.89*	−.14		
Strial atrophy	.68	−.12	−.25	.20	
Total spiral ganglion cell count	−.87*	.45	−.56	.34	−.44
Group 2					
Inner hair cell loss	.24				
Pillar cell loss	.39	.96†			
Outer hair cell loss	.32	.98†	.93†		
Strial atrophy	.07	.83*	.86*	.70	
Total spiral ganglion cell count	−.55	−.15	−.37	−.07	−.43
Group 3					
Inner hair cell loss	−.57				
Pillar cell loss	−.55	.92†			
Outer hair cell loss	−.62	.93†	.99†		
Strial atrophy	.01	−.29	−.29	−.35	
Total spiral ganglion cell count	.26	−.66	−.36	−.34	−.05

Two-tailed significance levels of correlation coefficients for sample size 6.

*Significant at 5% level (≥.81).

†Significant at 1% level (≥.92).

spiral ganglion cell count in the nondeafened ears was 25,644, compared to 5,543 in the affected ears of group 3 (Table 2). Thus, the spiral ganglion cell counts of both groups 2 and 1 (ISSHL with or without a viral prodrome) differ from that of group 3 (presumptive postnatal viral labyrinthitis), suggesting at least different target cells and perhaps a different cause of disease. Given the lack of significant correlation between spiral ganglion cell count and duration of deafness and the lack of significant difference in duration of deafness between groups 1 and 3, the difference in spiral ganglion cell count cannot be reasonably ascribed to delayed degeneration after onset of the hearing loss. It is reasonable to assume that the presence of residual hearing in group 2 partially accounted for the large differences in hair cell and pillar cell loss between this group and groups 1 and 3. By extrapolation, it may be conjectured that the cochlear hair cell and pillar cell losses in the three ears with partial hearing loss would have been more severe had the hearing loss been profound.

Three possible explanations for the dissimilarities in ganglion counts between ISSHL (group 1) and presumptive viral labyrinthitis (group 3) can be offered.

1. Perhaps ISSHL is due to non-neurotropic viruses (eg, adenovirus, influenza, parainfluenza virus, or rhinovirus). The neurotropism of cytopathic viruses like herpes, mumps, and measles could account for the severe neuronal atrophy seen in group 3.

2. Perhaps differences in target cells between ISSHL and postnatal viral labyrinthitis are due to a difference in the route of invasion rather than a difference in causation or viral strains. It may be that group 3 viruses attack the inner ear by both hematogenic and meningogenic (cerebrospinal fluid) routes, ie, a dual pathway, the former route resulting in organ of Corti, tectorial membrane, and strial degeneration and the latter route in ganglion cell atrophy. Putative viral infection in group 1 and 2 viruses, on the other hand, may reach the inner ear by hematogenic spread only and thereby account for lack of neuronal loss. The evidence in favor of a dual pathway theory for group 3 viruses is inconclusive. In the present study, only one of six cases in this group had clinical evidence of meningoencephalitis. Further evidence against meningogenic spread comes from the study of Azimi et al,[37] in which none of 51 patients with laboratory-proven mumps meningoencephalitis developed hearing impairment.

3. Perhaps ISSHL and postnatal viral labyrinthitis indeed have different causes. Thus, on the basis of the present histologic data of counts of residual spiral ganglion cells in groups 1 and 3, there is doubt cast on the theory of viral causation of ISSHL.

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Ann Otol Rhinol Laryngol 99:1990

CONVERSION BETWEEN SYSTEMS OF HEARING HANDICAP MEASUREMENT: AN EMPIRICALLY DETERMINED COMPUTATIONAL PROCEDURE

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Audiograms collected from 821 individuals were used to determine the interrelationships among five systems of determining hearing handicap based upon pure-tone thresholds. These were the American Academy of Ophthalmology and Otolaryngology, the British Association of Otolaryngologists and the British Society of Audiology, the American Medical Association, the industrial, and the full-range averages. A high degree of correlation (average r = .981) was found among the various indices. Using the regressions between all possible pairs of indices, we constructed a table that allows conversion between the various systems involving only very simple computation.

KEY WORDS — audiograms, audiology, hearing, hearing handicap, measurement, pure tone, thresholds.

The most widely used approach to the assessment of hearing disability involves reliance on the correlation between manifest disability and measures of impairment, namely pure-tone air conduction thresholds.[1] It has become a common practice to estimate hearing disability through the use of some formula based upon threshold data. As Noble[2] pointed out in his comprehensive review of the literature, many studies have dealt with these formulas. Most of these studies have addressed the issue of which audiometric frequencies should be included in such formulas, whereas some have attempted to derive specific weights for particular frequencies tested. Several of these formulas have achieved the status that they have been approved by various governmental agencies for use in determining compensation for hearing loss.[2,3]

Perhaps the most widely used system is that advocated by the American Academy of Ophthalmology and Otolaryngology.[4] This scheme (usually referred to as the AAOO formula) involves use of the frequencies 0.5, 1, and 2 kHz, and has been adopted by 14 states in the United States and also by Canada, Denmark, Iran, Israel, Japan, and Brazil. Another widely used system is the so-called American Medical Association (AMA) formula,[5] which uses the frequencies 0.5, 1, 2, and 4 kHz, and which has been adopted by two states in the United States and also by Australia and Italy. Traditionally, audiologists in the United Kingdom have used a formula with the frequencies of 0.5, 1, and 3 kHz. Recent recommendations from the British Association of Otolaryngologists and the British Society of Audiology[6] include the use of a formula based upon 1, 2, and 4 kHz (the BAOL/BSA formula), which is now achieving a broad acceptance in the United Kingdom. A measure that was formerly used by the Veterans Administration in the United States was a system based upon the frequencies 0.25, 0.5, 1, 2, and 4 kHz.[7] This system, referred to herein as the industrial formula, has been used as the measure in a number of industrial settings and court cases.[2] Recently, Coren,[8] on the basis of empiric evidence that considered the intercorrelations among the pure-tone thresholds for the six standard audiometric test frequencies (0.25, 0.5, 1, 2, 4, and 8 kHz), recommended that a full-range average of these frequencies be used, since such a measure (referred to herein as the full-range formula) has a mean correlation of .89 with the threshold for any of the individual audiometric frequencies.

It is not our purpose to resolve the issue of which of these indices is the best measure of hearing disability. We wish to address a more pragmatic problem; ie, the number and variety of the formulas used to assess hearing impairment represent a problem for the researcher or reader of the literature in that it is difficult to compare results obtained by means of one formula with those obtained by means of another. For instance, the low fence often recommended for the determination of hearing disability is an average pure-tone threshold, computed via the AAOO formula, exceeding 25 dB re International Standards Organization audiometric zero. Noble[2] reported that in Italy the officially set low fence is 20 dB computed via the AMA formula. Since the two determinations of hearing disability are based upon different subsets of frequencies, it is difficult to compare these two values to determine whether they represent comparable cutoffs. It is also impossible to translate these figures into the values expected from the BAOL/BSA, industrial, or full-range formulas for summarizing hearing performance. It should be possible to develop empirical formulas, however, that could allow conversion from one measurement system to another. To test the feasibility of this conversion, we conducted the following experiment.

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TABLE 1. CORRELATIONS BETWEEN PAIRS OF VARIOUS RECOMMENDED PURE-TONE AVERAGES USED FOR DETERMINATION OF HEARING HANDICAP (N = 821 SUBJECTS)

	AAOO	*BAOL/BSA*	*AMA*	*Industrial*	*Full-Range*
AAOO	—	.957	.979	.986	.961
BAOL/BSA		—	.994	.980	.985
AMA			—	.995	.989
Industrial				—	.985
Full-range					—

All correlations significant with $p < .001$.

For all tables, AAOO — American Academy of Ophthalmology and Otolaryngology[4] (0.5, 1, and 2 kHz), BAOL/BSA — British Association of Otolaryngologists and the British Society of Audiology[6] (1, 2, and 4 kHz), AMA — American Medical Association[5] (0.5, 1, 2, and 4 kHz), Industrial — see reference 7 (0.25, 0.5, 1, 2, and 4 kHz), Full-Range — see reference 8 (0.25, 0.5, 1, 2, 4, and 8 kHz).

TABLE 2. CONVERSION COEFFICIENTS TO CONVERT ONE PURE-TONE THRESHOLD INDEX TO ANOTHER

	Convert To				
Convert From	*AAOO*	*BAOL/ BSA*	*AMA*	*Indus-trial*	*Full-Range*
AAOO	—	1.172 (−5.59)	1.087 (−1.72)	1.041 (0.61)	1.138 (0.17)
BAOL/BSA	0.781 (5.85)	—	0.901 (3.87)	0.845 (6.23)	0.953 (5.87)
AMA	0.882 (2.25)	1.096 (−4.05)	—	0.946 (2.46)	1.055 (1.82)
Industrial	0.934 (−0.09)	1.137 (−6.49)	1.047 (−2.41)	—	1.105 (−0.73)
Full-range	0.811 (1.23)	1.018 (5.52)	0.927 (−1.31)	0.878 (1.21)	—

Multiply value obtained in original system by coefficient given, then add constant given in parentheses.

For abbreviations, see Table 1.

METHOD

Subjects. The sample consisted of 821 subjects (491 women and 330 men) who responded to advertisements in a university population and in the general community, and who were augmented by direct solicitation in several seniors groups. Subjects ranged in age from 17 to 92 years, with a mean age of 35.6 years. The grouped age distribution was 16 to 35 years, 435; 36 to 55, 164; 56 and older, 222. Information on occupation was not available for this sample.

Procedure. All subjects were tested individually in a sound-deadened room. A MAICO (MA-24) audiometer was used to obtain pure-tone air conduction hearing thresholds for six test frequencies: 0.25, 0.5, 1, 2, 4, and 8 kHz. Each ear was tested separately by standard audiometric procedures based upon an initial descending sequence of tones, followed by three ascending sequences with 5-dB steps. The median of the three ascending measures served as an estimate of threshold sensitivity for that ear.

RESULTS AND DISCUSSION

Since use of two audiograms from the same individual may lead to statistical confounding (Coren and Hakstian, unpublished observations, 1989), data analyses were arbitrarily limited to the right ear of each subject. A preliminary consideration of the data indicated a broad range of pure-tone threshold sensitivity in this heterogeneous sample. When hearing thresholds were averaged across the six test frequencies, values ranged from a minimum of 1.67 dB to a maximum of 110.0 dB.

For each subject each of the five indices (AAOO, BAOL/BSA, AMA, industrial, and full-range) was computed. The first question asked was how closely these indices were correlated. To this end, Pearson product-moment correlations were computed between all pairs of indices. These correlations are presented in Table 1.[4-8]

As can be seen from Table 1, the degree of association between the various indices is remarkably high, with an overall average correlation of .981. This means that there is, on average, approximately 96% shared variance between the indices. Such a close association was predictable on the basis of Coren's[8] finding that the average correlation between pure-tone thresholds for any pair of frequencies in the range 0.25 to 8 kHz was .89.

Although the correlations shown in Table 1 indicate that each of the five alternative indices measures virtually the same thing, this does not mean that the actual numeric value produced by each index is the same. There are scale differences among these measures that will require consideration when one is attempting to convert the value obtained by one index to the value expected for another. To determine the conversion coefficients, we computed a series of regression equations. Each of the indices was designated as the dependent variable in a bivariate regression equation with each of the other indices (considered separately) as the predictor. The resultant regression coefficient (slope) and additive constant (y-intercept) are reported for each of these equations in Table 2.[4-8]

Table 2 is designed to facilitate conversion from any one index to any of the others. To convert from one scale to another, one can simply multiply the index value by the regression coefficient listed in Table 2, and then add the constant, which is listed in parentheses. Thus, to find the BAOL/BSA equivalent of an AAOO score of 25 dB loss, one would multiply the AAOO score by 1.172 and then add −5.59, to achieve an expected value of 23.7 dB. As a further example, Table 3[4-8] presents the AAOO cutoffs for various degrees of handicap and the corresponding conversions into the other indices.

As can be seen from Table 3, the values computed around the lowest cutoff (25 dB loss) are quite close for the five indices. The largest discrepancy from 25 is less than 4 dB and hence is within one audiometric testing step. The differences between the various

TABLE 3. SAMPLE CONVERSIONS FROM AAOO TO OTHER SYSTEMS FOR AAOO HEARING HANDICAP CLASSIFICATION HURDLES IN DECIBELS THRESHOLD RE INTERNATIONAL STANDARDS ORGANIZATION

AAOO	*Degree of Handicap*	*BAOL/BSA*	*AMA*	*Industrial*	*Full-Range*
25	Slight	23.7	25.5	26.6	28.6
40	Mild	41.2	41.8	42.3	45.7
55	Marked	58.9	58.1	57.9	62.8
70	Severe	76.5	74.4	73.5	79.8
90	Extreme	99.9	96.1	94.3	102.6

For abbreviations, see Table 1.

indices become more marked as the degree of hearing handicap becomes greater. Thus, we see that at 90 dB, the AAOO scale underreports handicap relative to the other four indices. For the BAOL/BSA and the full-range scales, these discrepancies hover around 10 dB, or two full audiometric testing steps.

As a test of the accuracy and generality of these predictive equations, an independent sample of 154 audiograms, which had previously been collected for a different purpose (Coren and Hakstian, unpublished observations, 1989), was subjected to analysis. This sample consisted of 91 women and 63 men, with a mean age of 29.9, with a mean pure-tone hearing threshold (by use of the full-range computation) going from −5 dB to 86 dB re International Standards Organization. For each individual, each of the initial five indices (AAOO, BAOL/BSA, AMA, industrial, and full-range) was computed for the right ear only, and then the 20 possible conversions were computed by use of the figures in Table 2. The difference between the predicted and the actual values for each subject was then determined. Table 4[4-8] presents the percentage of subjects for whom the converted scores fall within one audiometric step (±5 dB) of the actual scores. As can be seen from Table 4, the agreement between the empiric conversion equation and actual test data is quite good. It approximates the test-retest reliability of pure-tone threshold testing as reviewed by Noble,[2] which is a bit over one audiometric step.

TABLE 4. CONVERSION ACCURACY USING PROCEDURES IN TABLE 3, FOR SAMPLE OF 154 SUBJECTS

Started From	*Converted To*				
	AAOO	*BAOL/BSA*	*AMA*	*Industrial*	*Full-Range*
AAOO	—	91.6 (141)	92.2 (142)	98.1 (151)	87.7 (135)
BAOL/BSA	88.3 (136)	—	98.7 (152)	91.5 (141)	92.2 (142)
AMA	92.2 (142)	99.3 (153)	—	100.0 (154)	98.1 (151)
Industrial	97.4 (150)	92.2 (142)	99.3 (153)	—	94.2 (145)
Full-range	90.3 (139)	92.8 (143)	98.1 (151)	93.5 (144)	—

Table entries indicate percentage of sample that falls within one audiometric step (±5 dB) of empiric values for each individual subject. Entries in parentheses indicate number, out of 154, that are correctly converted according to above criterion.

For abbreviations, see Table 1.

This report has attempted to provide a demonstration of how one can create a simple means to compare values obtained via various hearing handicap scales with use of empiric regression procedures. In this report, based upon the data from 821 subjects, we created a table (Table 2) that provides the coefficients that permit rapid conversion among the AAOO, BAOL/BSA, AMA, industrial, and full-range scales on the basis of pure-tone thresholds. Overall, there is a high degree of correlation among the various scales. The differences in obtained absolute values, however, become larger with larger degrees of hearing loss. Through the use of the computational procedures presented here, researchers and practitioners should be able to compare more easily results that are reported in one system with those reported in another. Similar procedures to those used in this report could be used to create conversion scales for any other audiometric systems. As long as one of the scales in such later studies overlaps one used in the present study, conversion to any of the other scales can be "bootstrapped" from Table 2 via a simple set of mathematical procedures. Until such time as there is a universally agreed-on scale for the measurement of hearing handicap, this will at least allow conversion from any one system to any other of interest.

ACKNOWLEDGMENTS — The authors thank Wayne Wong, Joan Donelly, Geof Donelly, and Dereck Atha, who assisted in the collection of data.

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Ann Otol Rhinol Laryngol 99:1990

MICROBIOLOGY OF "NORMAL" TONSILS

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Core tonsillar cultures for aerobic and anaerobic bacteria were performed on four normal tonsils removed from four children because of velopharyngeal insufficiency and on four tonsils removed from four children because of recurrent tonsillitis. The data illustrate the presence of polymicrobial flora in the cores of normal noninflamed tonsils and the increase in their number and encapsulation during the inflammatory process.

KEY WORDS — anaerobic bacteria, *Bacteroides* spp, β-lactamase, capsule, tonsillitis.

INTRODUCTION

Several studies have demonstrated the polymicrobial aerobic and anaerobic bacterial flora and the presence of β-lactamase–producing bacteria (BLPB) in the core of tonsils removed from children with recurrent group A β-hemolytic streptococcal (GABHS) tonsillitis[1-4] and tonsillar hypertrophy.[5] However, none of these studies evaluated the microbiology of "normal" tonsils removed from children without the history of any inflammatory conditions.

This report compares the quantitative microbiology of core tonsillar specimens from four children who had their tonsils removed because of anatomic reasons with the microbiology of four tonsils removed from four children with recurrent GABHS tonsillitis. This study provides insight into the question of whether there are any bacteria present in "normal" noninflamed tonsils.

PATIENTS AND METHODS

The tonsils studied prospectively were removed from four patients who had their tonsils removed because of velopharyngeal insufficiency that caused them speech problems (group 1), and from four patients who had their tonsils removed because of recurrent GABHS tonsillitis (group 2).

Children's ages ranged from 5 years 6 months to 12 years 10 months (mean age, 9 years 6 months), and all were boys. The age distribution was similar in both groups. None of the patients in group 1 had a history of recurrent tonsillitis or received antimicrobial therapy for at least 30 days prior to operation. The tonsils were noninflamed and were of normal size. However, these patients all had a history of one to two upper respiratory tract infections per year, and all had received therapy with a penicillin or a cephalosporin.

All of the children in group 2 suffered from recurrent tonsillitis, defined as a disease of at least 2 years' duration, with at least three episodes of inflammation of the tonsils within the last year. The duration of the patients' symptoms ranged from 2 to 5 years (average, 2.8 years). They received multiple courses of antibiotics, but none received any antimicrobial therapy for at least 1 month prior to operation.

Immediately after excision, one of the tonsils was placed in a sterile Petri dish and held by forceps. One side of the tonsil was cauterized with a heated scalpel, and an incision was made through that area, cutting the tonsil in half. A piece of the core of the tonsil was excised and placed in an anaerobic transport medium (Port-A-Cul swab system, BBL Microbiology Systems, Cockeysville, Md). The time between removal of the tonsils and inoculation of the specimen was never in excess of 24 hours. This system of transportation of specimens was chosen because of the data that show the efficacy of this mode of transportation in preserving aerobic and anaerobic bacteria qualitatively and quantitatively for at least 48 hours.[6] Quality control studies done prior to the study demonstrated the survival of organisms up to 48 hours.

The tonsillar tissue was weighed and homogenized in tenfold dilutions and was inoculated onto duplicate 5% sheep's blood, chocolate, and MacConkey agar plates for the isolation of aerobic and facultative organisms. The plates were incubated at 37°C aerobically (MacConkey agar) or under 5% carbon dioxide and examined at 24 and 48 hours. For anaerobes, the material was plated onto duplicate prereduced vitamin K1-enriched brucella blood agar plate, an anaerobic blood agar plate containing kanamycin and vancomycin, and an anaerobic blood agar plate containing phenylethyl alcohol and an enriched thioglycolate broth (containing hemin and vitamin K1). The anaerobic plates and thioglycolate broth were incubated in GasPak jars (BBL Microbiology Systems) and examined at 48 and 96 hours. Anaerobes were iden-

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ORGANISMS ISOLATED IN CORES OF FOUR "NORMAL" TONSILS AND FOUR RECURRENTLY INFLAMED TONSILS

	"Normal" Tonsils		*Recurrently Inflamed Tonsils*	
Organisms	*No. of Isolates*	*Mean No. of Organisms in 1 g (log10 CFU±SD)*	*No. of Isolates*	*Mean No. of Organisms in 1 g (log10 CFU±SD)*
Aerobic bacteria				
α-Hemolytic streptococci	4	4.2±0.9	4	4.8±0.2
γ-Hemolytic streptococci	2	3.6±0.6	3	4.5±0.5
Group A β-hemolytic streptococci	1	5.2	3	6.4±0.3
Group C β-hemolytic streptococci	1	5.1	—	—
Staphylococcus aureus	2 (2)	4.9±0.4	2 (2)	6.8±0.4
Branhamella catarrhalis	1	5.6	2 (1)	6.0±0.5
Hemophilus parainfluenzae	1	4.6	1 (1)	4.2
Subtotal	12 (2)		15 (4)	
Anaerobic bacteria				
Peptostreptococcus sp	4	5.8±1.4	4	7.3±0.8
Veillonella parvula	1	5.3	2	5.0±0.3
Bifidobacterium adolescentis	1	4.6	—	—
Lactobacillus sp	1	3.8	—	—
Fusobacterium sp	2	4.8±0.5	3	6.9±0.5
Fusobacterium nucleatum	2	6.0±1.0	3	8.8±0.6
Bacteroides sp	1	6.3	2	9.2±1.0
*Bacteroides melaninogenicus**	2 (1)	5.8±0.5	2 (2)	8.9±0.2
*Bacteroides asaccharolyticus**	1 (1)	7.1	3 (1)	8.6±0.5
*Bacteroides intermedius**	3	6.8±0.8	2 (1)	9.0±0.3
Bacteroides oralis	1	7.2	2 (2)	8.4±0.7
Bacteroides oris-buccae	1 (1)	6.9	2 (1)	8.2±0.8
Bacteroides distasonis	1	7.0	—	—
Bacteroides fragilis	—	—	1 (1)	8.0
Subtotal	21 (3)		26 (8)	
Total isolates	33 (5)		41 (12)	

Numbers of β-lactamase–producing bacteria are in parentheses.
CFU — colony-forming units.
**Bacteroides melaninogenicus* group.

tified by techniques previously described.[7] Aerobic bacteria were identified by conventional methods.[8] The β-lactamase activity was determined on all organisms by the chromogenic cephalosporin analog 87/312 method.[9] The presence of a capsule in the *Bacteroides melaninogenicus* group was established by the Hiss capsule stain[8] and confirmed by electron microscopy after staining with ruthenium red.[10]

The geometric means and standard errors of the means were calculated and compared by *t* test.

RESULTS

Thirty-three organisms (12 aerobes or facultative anaerobes and 21 strict anaerobes) were isolated from the "normal" tonsils (group 1; see Table). Mixed flora were present in all the tonsils, yielding an average of 8.25 isolates per tonsil (3.0 aerobes or facultative anaerobes and 5.25 anaerobes). Forty-one isolates (15 aerobes or facultative anaerobes and 26 strict anaerobes) were recovered from the recurrently inflamed tonsils (group 2). Mixed flora were isolated in all the tonsils, yielding an average of 10.25 isolates per tonsil (3.75 aerobes or facultative anaerobes and 6.5 anaerobes).

The numbers of some bacteria were about 100 to 1,000 times higher in the recurrently inflamed tonsils as compared to the "normal" tonsils. However, because of the small number of some isolates, significant differences ($p < .05$) were noticed only between all β-hemolytic streptococci, all *Bacteroides* spp, and all *Peptostreptococcus* spp. The aerobic organisms most frequently isolated from both groups were *Streptococcus* spp and *Staphylococcus aureus*. The predominant anaerobic organisms were *Bacteroides* spp, *Fusobacterium* spp, and anaerobic gram-positive cocci.

Organisms belonging to the *B melaninogenicus* group were present in all patients in both groups (see Table). However, only one of the six *B melaninogenicus* group isolates in group 1 was encapsulated, as compared to six of the seven in group 2 ($p < .025$).

β-Lactamase production was detectable in five isolates recovered from three of the four tonsils in group 1 and in 12 isolates recovered from all four tonsils in group 2. The BLPB were *S aureus* and *Bacteroides* spp.

DISCUSSION

This study illustrates that the cores of "normal" tonsils of children without a history of recurrent tonsillitis or tonsillar hypertrophy contain polymicrobial aerobic and anaerobic bacterial flora, some of which produces the enzyme β-lactamase. The organisms isolated from these normal tonsils are similar to those isolated from the core of tonsils of patients with a history of recurrent inflammation due to either group A[1,11] or non-group A[5,12] streptococci. However, the concentration of most of the anaerobic bacteria, as well as streptococci and staphylococci, was higher in recurrently inflamed tonsils. Similar to Kielmovitch et al,[12] we were also able to determine the number of organisms in the cores of inflamed tonsils. Differences in technique may explain the higher concentration of anaerobic bacteria detected in our study.

The recovery of similar polymicrobial aerobic and anaerobic bacterial flora from the cores of normal tonsils and from recurrently inflamed tonsils is a perplexing finding. A possible explanation is that these organisms that colonize the surface of normal tonsils[11,13] are also colonizers of the core of tonsils. However, since many of these organisms are potential tonsillar pathogens,[14] they may have a role in the inflammatory process that occurs in these tonsils. Whether the presence of these bacteria in the core of "normal" tonsils contributes to any pathologic process in these tonsils is yet to be determined. However, the increase in the number of several species of these organisms 100- to 1,000-fold in chronically inflamed tonsils suggests that these bacteria may contribute to the inflammatory process of recurrent tonsillitis.

The finding of more encapsulated *B melaninogenicus* group isolates in recurrently inflamed tonsils, as compared to normal tonsils, also supports the potential pathogenic role of these anaerobic bacteria. Encapsulation of *Bacteroides* sp has been recognized as an important virulence factor that contributes to the inflammatory process.[15] Two studies support the importance of encapsulated anaerobic organisms in respiratory tract infections.[13,16] The presence of encapsulated and abscess-forming organisms that belong to the *B melaninogenicus* group was investigated in 25 children with acute tonsillitis and in 23 children without tonsillar inflammation (control).[13] Encapsulated organisms of the *B melaninogenicus* group were found in 23 of 25 children with acute tonsillitis versus 5 of 23 control children ($p<.001$).

The presence of encapsulated *Bacteroides* sp and anaerobic gram-positive cocci was investigated in 182 patients who had head and neck or chronic orofacial infections and in the pharynx of 26 individuals without inflammation.[16] Forty-nine of the patients had chronic otitis media, 45 had cervical lymphadenitis, 37 had chronic sinusitis, 24 had chronic mastoiditis, 10 had peritonsillar abscesses, and 12 had periodontal abscesses. Of the 216 isolates of *B melaninogenicus* and *Bacteroides fragilis* groups, *Bacteroides oralis*, and anaerobic cocci, 170 (79%) were found to be encapsulated in patients with chronic infections, compared with only 34 (35%) of 96 isolates recovered from control subjects ($p<.001$).

The recovery of a greater number of encapsulated anaerobic organisms in patients with acute and chronic orofacial infections as compared to the rate of encapsulation in the normal flora provides further support for the potential pathogenic role of encapsulated organisms and the possible conversion of nonencapsulated strains into encapsulated ones during the inflammatory process.

Staphylococcus aureus, GABHS, *Streptococcus pneumoniae*, and viruses traditionally are associated with tonsillar and peritonsillar infections. However, anaerobes also have been isolated from the tonsils of children with chronic recurrent GABHS tonsillitis[1,11] and peritonsillar[14] and retropharyngeal abscesses.[17]

We were able to detect BLPB in the tonsils of three of the four "normal" tonsils and in all four chronically inflamed tonsils. This finding is similar to previous data reported in children with recurrent GABHS tonsillitis[1-4,12] and tonsillar hypertrophy.[5,12] The presence of BLPB in the cores of normal tonsils may be attributed to previous antimicrobial therapy in these patients.

More studies are warranted to investigate further whether the flora isolated in the core of normal-appearing tonsils has any pathogenic role in the inflammatory process that may subsequently occur in the host.

ACKNOWLEDGMENTS — The authors thank Drs K. M. Grundfast and Y. Brook for providing some of the tonsils, Dr C. H. Dorsey for performing the electron microscopy, J. Perry for technical assistance, and M. G. Barreiro for secretarial assistance.

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Ann Otol Rhinol Laryngol 99:1990

HISTOLOGIC STUDY OF EUSTACHIAN TUBE CARTILAGE WITH AND WITHOUT CONGENITAL ANOMALIES: A PRELIMINARY STUDY

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We investigated histopathologically the development of the eustachian tube (ET) cartilage at a cellular level in individuals with and without congenital anomalies. Fourteen specimens were obtained from 14 individuals ranging in age from 24 weeks' gestation to 3 years who had cleft palate or trisomy 21 (Down) syndrome; the 49 specimens in the nonanomaly (control) group were from 49 individuals ranging from 26 weeks' gestation to 85 years of age. All temporal bone specimens included the ET and its accessory structures, and all were processed and stained with hematoxylin and eosin for histologic study in a routine manner. The number of cartilage cells in the midcartilaginous portion of the ET was determined by light microscopy. In all groups, cartilage cell density of the ET decreased with increasing age. However, cell density tended to be higher at all ages for individuals with cleft palate and microtia versus controls, and tended to be lower at all ages for individuals with Down syndrome.

KEY WORDS — cartilage cell, congenital anomaly, development, eustachian tube cartilage.

INTRODUCTION

The change that eustachian tube (ET) cartilage undergoes with growth has been postulated as an important factor in ET function, and the immature ET cartilage of infants may be related to ET dysfunction.[1] "Floppy" cartilage support has been postulated as a possible cause of ET dysfunction in infants.[2] This finding is especially notable in individuals with congenital anomalies affecting this area.[3,4]

Previous investigators reported that as the amount of interstitial material increases, the cartilage cells become isolated and gradually take on the cytologic characteristics of mature cartilage cells or chondrocytes.[5] This suggests that the density of the ET cartilage cells decreases as the cartilage becomes more mature. However, to our knowledge, no attempt has been made to compare the density of ET cartilage cells in individuals of different ages. As this may be an important factor in the development of ET cartilage, we measured the density of cartilage cells in individuals with and without congenital anomalies to determine how ET cartilage matures.

METHOD AND MATERIALS

A total of 63 temporal bone specimens that included the entire ET cartilage were used.[6] The 14 specimens in the anomaly group were from 14 individuals with congenital anomalies (11 with cleft palate and 3 with trisomy 21 [Down] syndrome), ranging in age from 24 weeks' gestation to 3 years. Four of the 11 individuals with cleft palate also had microtia. The 49 specimens in the control (nonanomaly) group were from 49 individuals ranging from 26 weeks' gestation to 85 years of age. Of these individuals, 24 were less than 3 years of age.

To determine the developmental age at death of the premature newborns, 40 weeks (regarded as full term) was subtracted from the sum of the infant's gestational age and period of life after birth. For example, an infant who was born after 36 weeks' gestation and who lived 8 weeks postnatally was said to be developmentally 4 weeks (1 month) old for the purpose of this study.

The temporal bone specimens were removed from cadavers at autopsy and were processed for histologic study in a routine manner; they were fixed in 10% formalin, decalcified in 5% trichloroacetic acid, dehydrated in graded solutions of ethanol, and embedded in celloidin. Serial vertical sections 20 to 30 μm thick were then cut perpendicular to the long axis of the petrous bone. Every 40th section was stained with hematoxylin and eosin and was examined under a light microscope.

Cartilage cells at all focal levels were counted in a 40,000-μm^2 region at three different sites in the center of the medial lamina of the midcartilaginous

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Presented at the Eleventh Midwinter Research Meeting of the Association for Research in Otolaryngology, Clearwater Beach, Florida, Jan 31–Feb 4, 1988.

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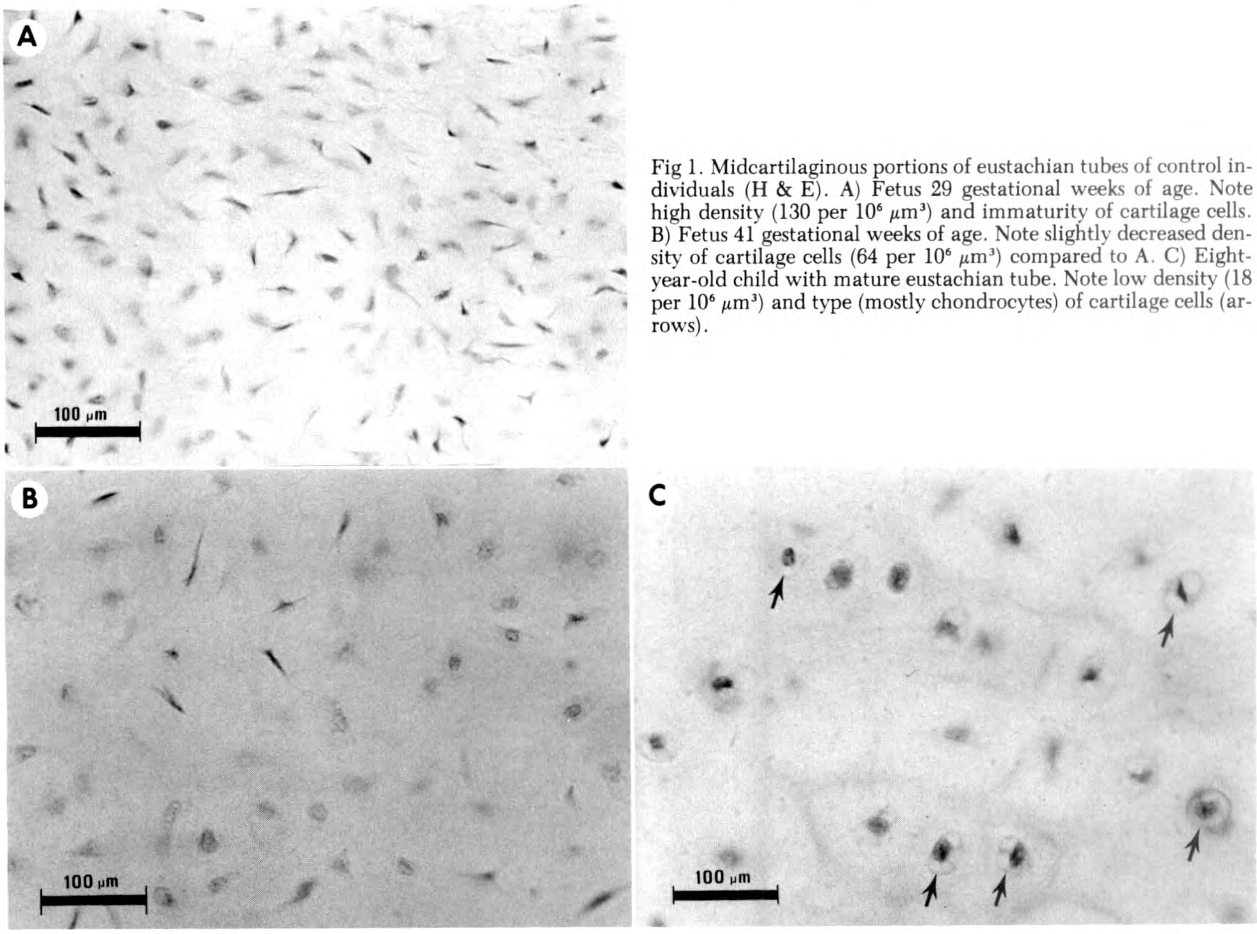

Fig 1. Midcartilaginous portions of eustachian tubes of control individuals (H & E). A) Fetus 29 gestational weeks of age. Note high density (130 per $10^6\ \mu m^3$) and immaturity of cartilage cells. B) Fetus 41 gestational weeks of age. Note slightly decreased density of cartilage cells (64 per $10^6\ \mu m^3$) compared to A. C) Eight-year-old child with mature eustachian tube. Note low density (18 per $10^6\ \mu m^3$) and type (mostly chondrocytes) of cartilage cells (arrows).

portion of the ET. The average of these three values was used to calculate the cell density per $10^6\ \mu m^3$, based upon the thickness of the sampled sections (20 or 30 μm).

We compared the densities of cartilage cells in the cleft palate group, the trisomy 21 group, and the control group.

RESULTS

Photomicrographs of ET cartilage cells in three control cases of different ages and in one cleft palate case are shown in Figs 1 and 2, respectively. As may be seen in these pictures, in the control cases (Fig 1) the density of cartilage cells decreased with increasing age, and the cell density in a cleft palate case (Fig 2) was higher than in a control case of similar age (Fig 1B).

Number of Cartilage Cells in Control Group. Figure 3 shows the number of ET cartilage cells as a function of age for control specimens. For individuals 24 to 30 gestational weeks old, the mean number of cartilage cells in $10^6\ \mu m^3$ was 126. The mean number of cells decreased rapidly with increasing gestational age and continued to decrease, although at a slower rate, with increasing postnatal age. There was a statistically significant difference in the number of ET cartilage cells between individuals younger than 7 years old (59.9 ± 29.2 per $10^6\ \mu m^3$) and those older than 8 years old (15.7 ± 4.4 per $10^6\ \mu m^3$) ($t = 7.169$, $p < .001$). The mean number of cells in specimens from individuals 8 to 12 years of age was already close to that of the adult specimens. Overall, there was a reciprocal relationship between the density of cartilage cells (Y) and age (X) in the control group: $Y = 50.55/(X + 0.83) + 12.20$ (coefficient of correlation = .93).

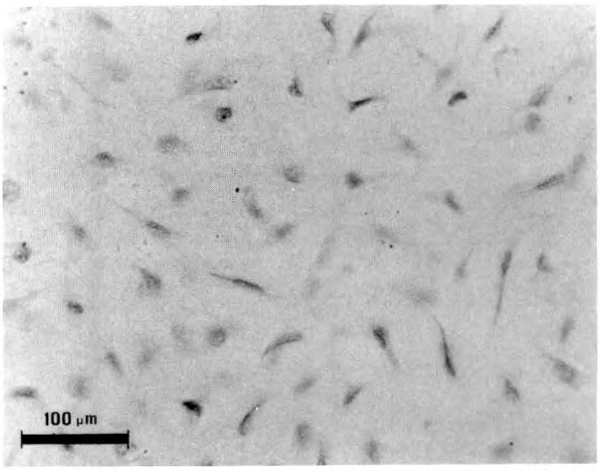

Fig 2. Midcartilaginous portion of eustachian tube cartilage of infant with cleft palate and microtia, 43 gestational weeks of age (H & E). Density of cartilage cells was 94 per $10^6\ \mu m^3$.

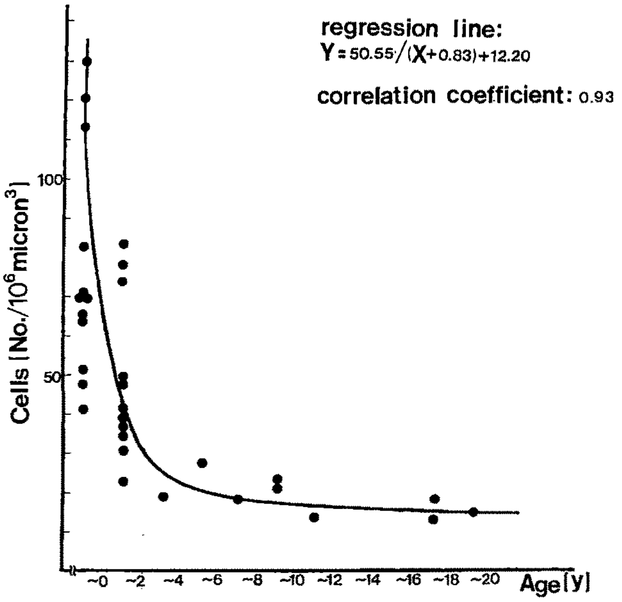

Fig 3. Number of eustachian tube cartilage cells as function of age for control cases. Ordinate represents number of cartilage cells in 10^6 μm^3 of eustachian tube cartilage at its midcartilaginous portion.

Number of Cartilage Cells in Anomaly Group. The density of cartilage cells in 11 individuals with cleft palate was compared with that of 24 control individuals in the same age range (Fig 4). Although there was no statistically significant difference between the two groups, the density of cartilage cells tended to be higher in the cleft palate cases than in controls. In particular, cell density was higher in the 4 individuals with both cleft palate and microtia than in controls. On the other hand, cell density in 3 individuals with trisomy 21 (Down) syndrome tended to be lower than in controls.

DISCUSSION

It has been reported that otitis media occurs more often in young infants than in older children,[7] that younger children have poorer ET function compared to older children,[8] and that active tubal ventilatory function in infants, especially under negative pressure, is poorer than in adults.[1] In this study, we noted a greater density of cartilage cells in younger infants. Our finding could indicate that the ET cartilage is immature in infants, which may result in its being hypercompliant or "floppy."[1] Immature, hypercompliant ET cartilage might not be able to support the ET adequately; this could be one reason for the ET ventilatory dysfunction seen so often among younger children. Our finding that cartilage cell density decreases to that seen in adults by 8 to 12 years of age agrees well with the decrease of otitis media noted in this age group.[7]

In addition to anomalies of the ET and its surrounding structures,[9,10] excessive compliance of the ET has been suggested as one of the causes of ET dysfunction in individuals with cleft palate. Bluestone et al[11] reported that infants with cleft palate cannot equilibrate negative middle ear pressure and have lower passive opening pressures than older individuals; this suggests that excessive compliance may be related to ET dysfunction. Our findings from this study showed that the ET cartilage in cleft palate infants is immature. It is suggested that this anatomic and physiologic immaturity of the ET in cleft palate infants could be one of the factors in ET dysfunction causing a high incidence of otitis media in this population.

The ET cartilage was also found to be immature in individuals who had both cleft palate and micro-

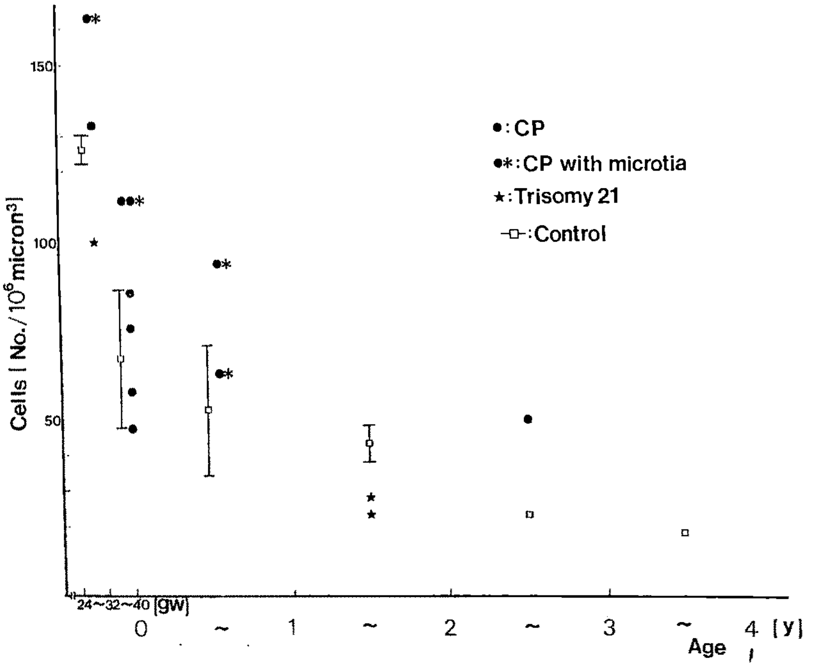

Fig 4. Density of eustachian tube cartilage cells as function of age for individuals with cleft palate (CP), CP with microtia, or trisomy 21 (Down) syndrome. Ranges for controls are also shown. gw — gestational weeks.

tia. This is to be expected from what we know about the phylogenetic development of the palate, the auricle, and the ET cartilage.[12] The palate is derived from the first branchial arch, which also contributes to the development of the auricle. In addition, the tensor veli palatini muscle, which attaches to the ET cartilage, is derived from the first branchial arch. The ET is derived from the first pharyngeal pouch. These derivations make it likely that ET cartilage is derived from the first branchial arch, although so far as we know there has not yet been a study of the derivation of ET cartilage. Should the foregoing relationships hold true, we might expect individuals with cleft palate and anomalies of structures originating from the first and second branchial arches to often have immature ET cartilage as well, resulting in more frequent otitis media due to ET dysfunction.

The low density of ET cartilage cells in individuals with trisomy 21 syndrome is interesting in the light of reports by others[13-15] that heart and skeletal muscle cells are less dense in such individuals. Landing and Shankle[14] reported that a biochemical "signal" relating to chromosome 21 determines the numbers and sizes of cells and shuts off cellular multiplication in Down syndrome when the number of cells is two thirds the normal number. Further investigation of this phenomenon and its effect on function of the ET could contribute significantly to our understanding of this clinically important pathologic condition.

In conclusion, the results of this study lead us to speculate that immaturity of the ET cartilage in infants and those with congenital anomalies is related to one of the causes of ET dysfunction, which in turn results in more frequent cases of otitis media in these individuals. Development of the ET cartilage should be investigated further so that the relationships among otitis media, dysfunction of the ET, and ET cartilage abnormalities can be clarified.

ACKNOWLEDGMENTS — The authors thank Charles D. Bluestone, MD, Professor, and Eugene N. Myers, MD, Professor and Chairman, Department of Otolaryngology, University of Pittsburgh School of Medicine, for encouraging them to continue this project and for offering helpful criticism during this study. Appreciation is also given to Karen Milligan and Theresa Taylor for their kind assistance.

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Ann Otol Rhinol Laryngol 99:1990

CHANGES IN THE COCHLEAR IRON ENZYMES AND ADENOSINE TRIPHOSPHATASE IN EXPERIMENTAL IRON DEFICIENCY

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The influences of iron deficiency on the cochlear iron enzymes and adenosine triphosphatase were studied in 68 iron-deficient rats and 68 control rats (normal and with chronic anemia). A disorderly or topographic distribution and reduction or disappearance of the cochlear succinic dehydrogenase and peroxidase reaction products were found in 37.8% of the rats fed on a basic iron-deficient diet for 14 to 100 days. The activity of cochlear sodium-potassium-dependent adenosine triphosphatase in iron-deficient rats was slightly increased, compared to that in normal controls. These results suggest that iron deficiency would produce significant abnormalities of succinic dehydrogenase and peroxidase activity, which in turn would disturb cell respiration and initiate peroxidative damage to the inner ear cells, result in sensorineural hearing loss, or provide a pathologic basis for cochlear deafness.

KEY WORDS — inner ear, peroxidase, succinic dehydrogenase, tissue iron.

In our previous studies, we found that the serum iron levels of patients with sensorineural deafness were significantly lower than those of persons with normal hearing, and that most patients with sensorineural deafness whose hearing had been improved after iron treatment usually had raised serum iron levels, while there was no change in the iron levels in patients whose hearing failed to improve.[1] Electrophysiologic findings showed that the incidence of an auditory threshold elevation of more than 15 dB was 31.85% in iron-deficient rats, but it was unchanged in all the control animals. The main cochlear histopathologic changes induced by iron deficiency were strial atrophy and reduction of spiral ganglion cells.[2] When the organ of Corti of iron-deficient rats was examined by electron microscopy, abnormalities of outer hair cells (OHCs) or inner hair cells (IHCs) were found as follows: fusion and twisting of stereocilia, coalescence of adjacent stereocilia in the same row, loss of sensory hair stiffness, and loss of stereocilia.[3] This leads us to further consider the underlying mechanisms of cochlear changes induced by iron deficiency. The present work aims at studying the histochemical and biochemical changes in the cochleas of iron-deficient rats.

MATERIALS AND METHODS

Animals and Diets. Wistar albino rats between 21 and 25 days of age (30 to 45 g body weight) with normal Preyer's reflexes, auditory brain stem response, and electrocochleogram thresholds, none of which had been exposed to noise or ototoxic drugs, were used in the experiment. Moderate to severe iron deficiency was induced by providing the rats with a diet containing 8.96 mg iron as ferric sulfate per kilogram of the basic iron-deficient diet.[4] Control rats received the same diet supplemented with 250 mg iron per kilogram of the final iron-supplemented diet.

The rats were randomly divided into three groups. In group 1, 43 animals (22 males and 21 females) were given the final iron-supplemented diet and plain water for 7 to 100 days; these animals were used as standard controls.

In group 2, 25 animals (12 males and 13 females) used as chronic anemia controls were given the same diet and water as group 1, but received phenylhydrazine hydrochloride intravenously every 5 to 7 days for 7 to 100 days.

Sixty-eight animals (35 males and 33 females), allocated to group 3, were fed with the basic iron-deficient diet and demineralized water for 7 to 100 days, serving as the animal models of iron deficiency. Spontaneous otitis media was nonexistent in the studied rats.

Hematologic Study. Hemoglobin concentrations were determined on tail blood samples by the cyanmethemoglobin method.[5] Serum iron concentrations were determined by atomic absorption spectrophotometry.[6]

Iron Enzyme Histochemical Study. The animals were killed painlessly by decapitation following in-

TABLE 1. HEMATOLOGIC DATA (MEAN±SD)

	Group 1	*Group 2*	*Group 3*
Hemoglobin (g/dL)	14.18± 1.92	6.23± 2.43*	6.08± 2.41*
Serum iron (μg/dL)	235.87±32.64	246.79±29.85	62.45±28.78†

*Significantly different ($p<.01$) from group 1.
†Significantly different ($p<.01$) from groups 1 and 2.

From the Otolaryngological Laboratories (Sun, Xiao, Z.-J. Li, Wang) and the Department of Clinical Laboratory (J.-Y. Li), Changhai Hospital, Shanghai, People's Republic of China.

TABLE 2. SUCCINIC DEHYDROGENASE REACTIONS IN CELLOIDIN-SECTIONED ORGAN OF CORTI (NUMBER OF EARS)

Feeding Time (wk)	*Study Group*	*Reaction*				
		None	*Weak*	*Moderate*	*Strong*	*Very Strong*
1	1					
	2				8	
	3		2		6	
2-3	1		2		2	
	2			2	2	4
	3	6	2	3	1	
6-9	1			2	6	2
	2				4	5
	3	1	6	7	4	1
10-12	1					
	2				3	3
	3	1	2		3	

tra-abdominal injection of phenobarbitone, and both temporal bones were promptly removed. The procedure involved holding the cochlea between the curved blades of rongeurs and carefully increasing pressure until one or more cracks occurred. From these cracks pieces of bony cochlear wall were removed with fine forceps. Enzymatic activity was determined from celloidin sections and surface preparations stained for succinic dehydrogenase (SDH; Enzyme Commission No. 1.3.99.1) by the method of Nachlas et al,[7] and for peroxidase (Enzyme Commission No. 1.11.1.7), by the modified method of Novikoff and Goldfischer.[8] For controls, incubations were performed without substrate.

Biochemical Study of Adenosine Triphosphatase. After decapitation, temporal bones were removed and kept in an ice-cold 2.5-mmol/L solution of ethylenediaminetetraacetate (EDTA) adjusted to pH 7.5 with trishydroxymethylaminomethane (Tris). Under a stereoscopic microscope at 15x magnification, the bullae were opened, and the bony otic capsule was removed by dissection. The stria vascularis (SV), spiral ligament, and organ of Corti (1.5 to 3.0 mg cochlear tissue weight per ear) were removed and ground into homogenate. The protein concentration of the homogenate was determined by the method of Lowry et al.[9]

The assay of the sodium-potassium–adenosine triphosphatase (Na-K-ATPase; Enzyme Commission No. 3.6.1.3) activity was done within 90 minutes after death of the animals, essentially by a modification of the procedure of Sigström and Waldenström.[10] By this method, 100 μg of the homogenate protein was added to 1 mL of solution containing 1 mmol/L adenosine triphosphate (ATP; Tris salt), 1.5 mmol/L magnesium chloride, 60 mmol/L sodium chloride, 10 mmol/L potassium chloride, 0.25 mmol/L EDTA, and 30 mmol/L Tris hydrochloride of pH 7.4, with and without 0.5 mmol/L ouabain. Sample was mixed and incubated at 37°C for 1

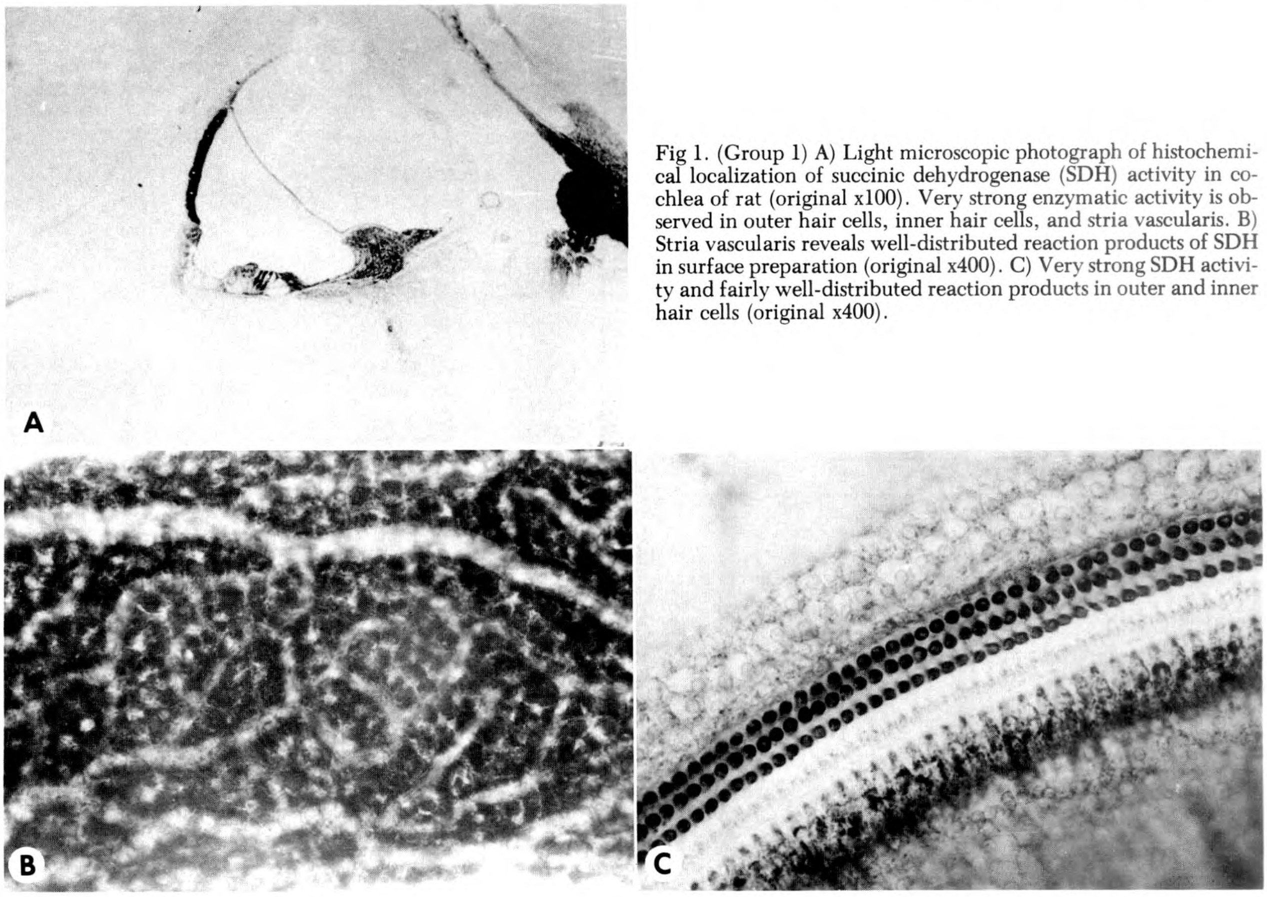

Fig 1. (Group 1) A) Light microscopic photograph of histochemical localization of succinic dehydrogenase (SDH) activity in cochlea of rat (original x100). Very strong enzymatic activity is observed in outer hair cells, inner hair cells, and stria vascularis. B) Stria vascularis reveals well-distributed reaction products of SDH in surface preparation (original x400). C) Very strong SDH activity and fairly well-distributed reaction products in outer and inner hair cells (original x400).

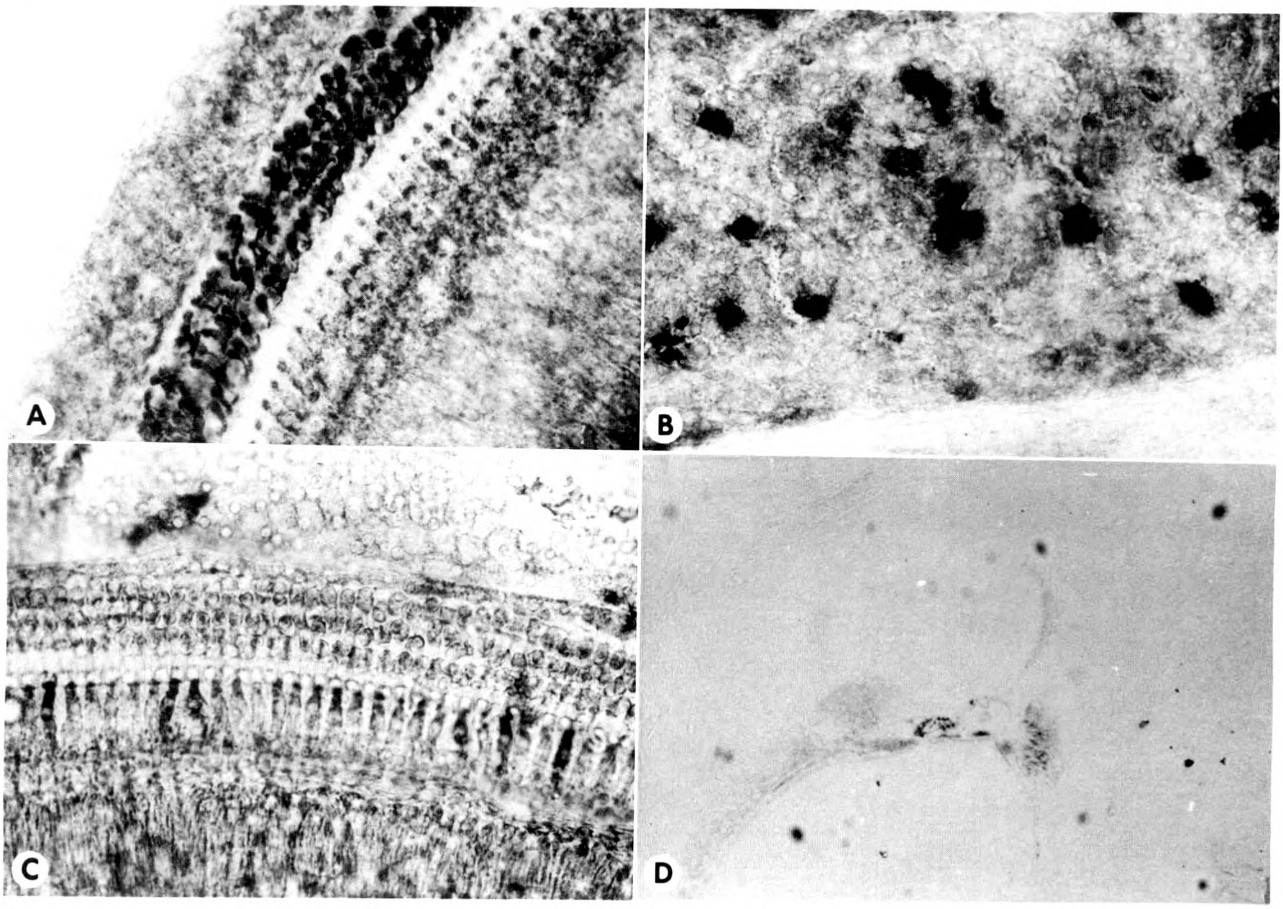

Fig 2. (Group 3) A) Disorderly distribution of succinic dehydrogenase (SDH) reaction products in outer hair cells of rat fed with basic iron–deficient diet for 10 days (original x400). B) Topographic distribution of SDH reaction products in stria vascularis at 12th week of iron deficiency (original x400). C) Negative or weak reaction in outer hair cells and disorderly distribution of SDH reaction products in inner hair cells at 10th week of iron deficiency (original x400). D) Weak SDH reaction in stria vascularis and very strong SDH reaction in outer and inner hair cells are seen at 6th week of deficit (original x100).

hour. The Na-K-ATPase activity was calculated by subtraction of ouabain-resistant ATPase activity from the total ATPase activity and expressed as inorganic phosphate nmol/L per minute per milligram of protein.

RESULTS

The hematologic findings are shown in Table 1.

Iron Enzymes. The results on the celloidin sections are summarized in Table 2. For both the celloidin-sectioned and surface preparation samples, a very strong or strong reaction was consistently observed in the OHCs, IHCs, and SV in the controls except for two animals. By contrast, variable changes in the degree of enzymatic activity were frequently seen in iron-deficient rats. At week 1, no significant change in the enzymatic activity was observed. After week 2, the disorderly or topographic distribution, reduction, and disappearance of enzymatic reaction products in IHCs, OHCs, and the SV were found in 37.8% of the animals (Figs 1 and 2A-C). The changes in enzymatic activity were obtained earlier in the SV than in the OHCs or IHCs (Fig 2D).

Peroxidase. The OHCs, IHCs, and SV of rats in both groups 1 and 2 showed a very strong or strong reaction, while the changes in activity of the enzyme were similar to that of SDH in group 3. Control incubations of SDH and peroxidase without substrate were always negative.

Adenosine Triphosphatase. The activity of cochlear Na-K–dependent ATPase in group 3 was slightly increased ($p < .2$) compared to that in group 1 (Table 3).

DISCUSSION

Although present in very small amounts in the body, iron plays an important role in many metabolic functions. Recent studies in animals and humans demonstrated that iron deficiency produces a reduction in the activity of iron-containing enzymes of cardiac muscle, brain tissue, and gastrointestinal mucosa, particularly SDH, monoaminoxidase, and cytochrome oxidase, by the 7th and 14th weeks.[11] In the red cells of iron deficiency anemia, the activities of various forms of ATPase were markedly decreased.[12] However, there is little information concerning the changes in these enzyme systems of the

TABLE 3. ADENOSINE TRIPHOSPHATASE BIOCHEMICAL DATA (MEAN±SE)

Study Group	*Feeding Time (d)*	*No. of Ears*	*Adenosine Triphosphatase (Pi nmol/L per minute per milligram)*		
			Dependent	*Basal*	*Total*
1	63	20	10.1866±2.4662	41.1530±6.0044	51.3396±5.0032
3	63	20	13.6285±2.7934	45.8956±7.0664	59.5241±8.1758
		p value	<.2	>.05	>.05

Pi — inorganic phosphate.

inner ear. The present investigation has shown that the decrease in the activity of SDH and peroxidase appeared at the end of the first week, and did not return even at week 12, in 37.8% of the cochleas of iron-deficient rats. By contrast, a slight increase in the activity of Na-K-ATPase, which appears independent of iron, was apparent at the ninth week of the deficiency. These findings suggest that the same iron-containing enzyme sometimes behaved in a different fashion in susceptibility to depletion of iron in different tissues, and that iron deficiency does not affect non–iron-containing enzyme activity such as that of Na-K-ATPase very much.

There are several experimental results that would lead us to believe that the abnormalities of iron-containing enzymes in the iron-deficient rats arise from effects of iron deficiency other than hemoglobin depletion. First of all, there seems to be little relationship between the severity of anemia and the degree of reduction in the activity of iron-containing enzymes. Many rats with mild iron deficiency anemia have a weak or negative enzymatic reaction; conversely, severely anemic rats may show a very strong or strong reaction. A second suggestive result is that the various degrees of reduction in the activity of iron-containing enzymes are not seen in the controls with chronic anemia. Third, a significant correlation was observed between the degree of reduction in the activity of iron enzymes and the serum iron levels. In other words, the abnormalities of enzymatic activity might be caused by the tissue iron depletion of the cochlea. Like the incidence of hearing loss,[2] changes in the activity of iron-containing enzymes occurred only in a small number of iron-deficient rats. The reason for this finding is unclear.

The histochemical finding that in the various parts of the cochlea, particularly in the SV and organ of Corti, the activity of iron enzymes such as SDH and peroxidase is extremely strong suggests that the inner ear is especially sensitive to iron deficiency. Succinic dehydrogenase is an enzyme that appears to contain nonheme iron and to play a very important role in mitochondrial respiration. As mentioned above, iron deficiency reduces SDH activity, thereby seriously disturbing cell respiration. Peroxidase is also one of the iron enzymes that have many essential biochemical functions in the body. As an intracellular scavenger, the function of peroxidase is to scavenge peroxide molecules and free radicals. Scavengers in normal cells include peroxidase, catalase, and vitamin E, which are shown to be reduced in iron deficiency.[13] A reduction of peroxidase activity in the cochlea must reduce the enzymatic detoxifying capacity for intracellular peroxide and increase peroxidative activity in the inner ear cells, resulting in the generation of reactive oxygen species that initiate peroxidative damage to the cochlear cells. Therefore, it is likely that both 1) the disturbance of cell respiration and peroxidative damage to the cells caused by the abnormalities of SDH and 2) peroxidase activity damage to cochlear structure and function result in sensorineural hearing loss, or provide a pathologic basis for cochlear deafness.

The elucidation of a slight increase in Na-K-ATPase activity in iron-deficient rats after 9 weeks of iron deficiency remains a task for the future.

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26TH POSTGRADUATE COURSE IN EAR SURGERY

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AGE-RELATED CHANGES IN EVOKED OTOACOUSTIC EMISSIONS

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Outer hair cells of the organ of Corti play an important part in the genesis of evoked otoacoustic emissions (EOAEs), which are related to cochlear biomechanics. The aim of this study was to investigate the age factor in relation to EOAEs in 166 ears of subjects between 6 weeks and 83 years of age. The results show that when age increases, the presence of EOAEs by age group and the frequency peak in spectral analysis decrease, and EOAE threshold increases. Thus, there is an effect of age upon EOAEs, and it seems linked with alteration of cochlear biomechanics and/or hair cell loss. Such an effect has to be taken into consideration when EOAEs are used in clinical applications, and limits the use of EOAEs in older subjects.

KEY WORDS — age, cochlear biomechanics, organ of Corti, otoacoustic emissions, outer hair cells.

The studies by Kemp[1] showed that acoustic emissions could be found in the human outer ear canal in response to acoustic clicks or to short tone-bursts. Kemp's findings have since been confirmed by several authors for humans[2-6] and monkeys.[7] Several arguments point to the conclusion that the outer hair cells (OHCs) of the organ of Corti play an important part in the genesis of evoked otoacoustic emissions (EOAEs).[8] Contractile structural proteins were identified in these cells,[9-11] and Flock[12] suggested that these may have motor capability. Brownell et al[13,14] showed changes in OHC length under electrical stimulation. Thus, there are active mechanical cochlear phenomena in the organ of Corti, and the present hypothesis is that OHCs modify mechanically, via the tectorial membrane, transduction phenomena in the inner hair cells of the organ of Corti.[15-18] Damage to OHCs is associated with a drop in or disappearance of EOAEs under noise exposure, ototoxic drug treatment, or anoxia.[8,19] The inner mechanism of EOAEs, however, remains unknown, although there have been a number of hypotheses.[19-21] The OHCs nevertheless do underlie EOAEs. There is a cell loss with age.[22] As the progressive decrease concerns outer more than inner hair cells,[23] it would seem reasonable to investigate the age factor in relation to EOAEs. Bonfils et al[24] have shown a decrease in EOAE incidence in subjects more than 60 years old. Such work needs to be replicated to confirm those results and to obtain normative data.

METHOD

Subjects. The study involved 166 ears from 93 subjects between 6 weeks and 83 years of age (mean = 33.5 years; SD = 20.71), with no history of auditory disease, who were audiometrically normal. Brain stem auditory evoked potentials were recorded from those children too young to complete the audiometric test.

Recordings. Otoacoustic emissions were recorded with a small probe consisting of a Tandy WM 063 T microphone and a Knowles K 2912 earphone. A small tube was used between the microphone and the orifice of the probe. The recordings were carried out in a soundproof room with subjects lying down to limit muscular interference. The stimulus was an unfiltered rarefaction click (100 microseconds), the analysis time was 40 milliseconds over 512 points, and the click rate was 22.7 per second. The number of trials was 1,000. A pass band of 200 to 7,000 Hz was used. The amplification was x40,000. Stimulus presentation, data recordings, averaging, and spectral analysis were carried out by a Nicolet Pathfinder II apparatus.

The level of the stimulus was from 40 dB hearing level (HL) (normal click threshold) to the EOAE threshold (10-dB steps; 5-dB near threshold). The procedure was first a descending method, and then below the threshold an ascending method was used.

Measurements. The EOAEs were counted as present if they met with criteria for latency (greater than 6 milliseconds), reproducibility of waveforms and of spectral analysis (appreciated by the superposition of waveforms and of spectral analysis), and nonlinear saturation (ie, saturation of responses to higher stimulus levels).[25] We noted presence of EOAEs, threshold (minimum stimulus acoustic intensity) for EOAEs, subjective click perception threshold, and the frequency of the highest frequency peak at 30 dB HL in spectral analysis.

Statistical Analysis. We applied analysis of variance (ANOVA), Student's *t* test, and the Pearson correlation coefficient calculation. Correlation co-

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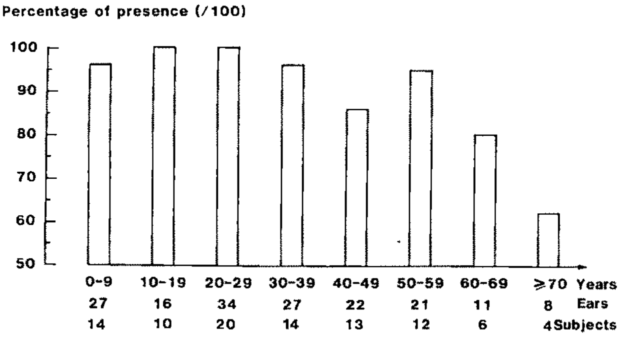

Fig 1. Presence of evoked otoacoustic emissions according to age group.

efficients were compared according to the hyperbolic tangent argument.[26]

RESULTS

Left Versus Right Ear. The study involved 146 ears, ie, 73 subjects underwent bilateral testing. No significant differences were found for presence of EOAEs on the right (mean = 95.89%) or the left (mean = 89.04%), subjective threshold (8.67 dB HL, right; 9.29 dB HL, left: matched $t = 0.79$, not significant [NS]), EOAE threshold (4.20, right; 5.15, left: matched $t = 0.83$, NS), or frequency peaks (1,193 Hz, right; 1,190 Hz, left: matched $t = 0.056$, NS). This absence of intrasubject left-right difference allows us to apply statistical calculation to all the ears tested.

Presence of EOAEs by Age Group. In 155 of the 166 ears, EOAEs were present. They were almost constantly found up to the age of 60 years (between 86% and 100% of ears tested in each 10-year age range) (Fig 1). Above the age of 60, this result drops off. An age effect relating to presence of EOAEs according to age group is shown in the ANOVA: F (8,157) = 3.14 ($p < .01$). There is no difference between males (93.6%) and females (93.2%).

Age Factor for EOAE Threshold. A significant age-related effect upon EOAE thresholds has been found (Fig 2): F (8,146) = 8.13 ($p < .0001$). The Pearson correlation coefficient between age (in years) and EOAE threshold is .17 (N = 155; $p < .05$). The subjective click threshold was measured only in 148 ears because of the difficulty of testing it in young children.

Age Factor for Subjective Click Perception Threshold. Figure 3 shows that there is an age-related effect upon subjective click perception thresholds: F (8,139) = 42.56 ($p < .0001$). The correlation coefficient between subjective threshold and age is .69 (N = 148; $p < .0001$).

Comparison Between Correlations for Subjective Threshold and Age and EOAE Threshold and Age. This calculation was made by use of the hyperbolic tangent argument. Age was found to correlate significantly more closely with the subjective perception threshold than with that for EOAE: z = 5.8 ($p < .0001$).

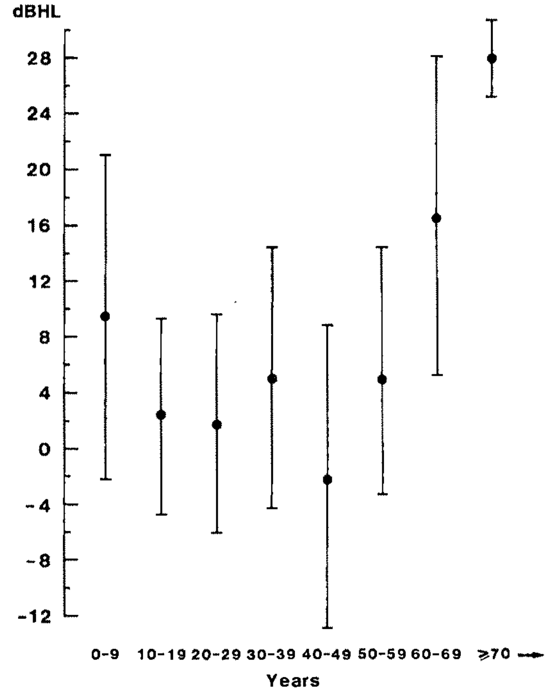

Fig 2. Evoked otoacoustic emission threshold according to age group.

Figure 4 shows a connection between EOAE an subjective thresholds (N = 138): F (8,127) = 5.8

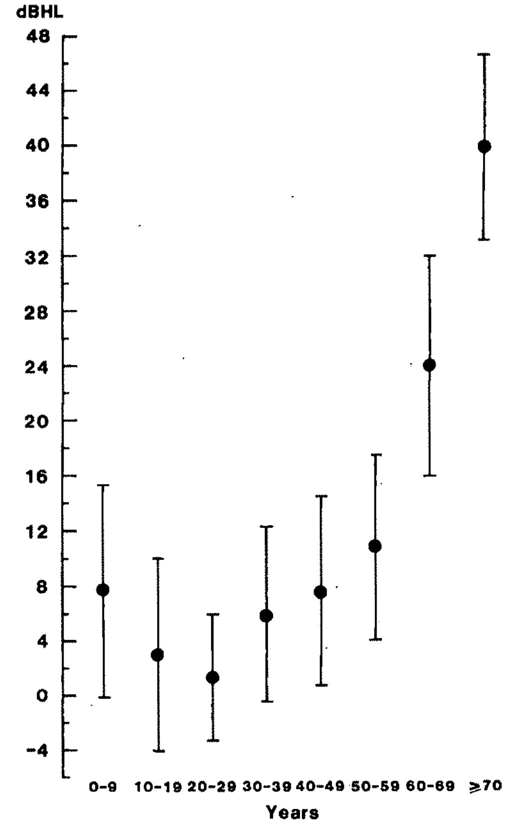

Fig 3. Subjective threshold according to age group.

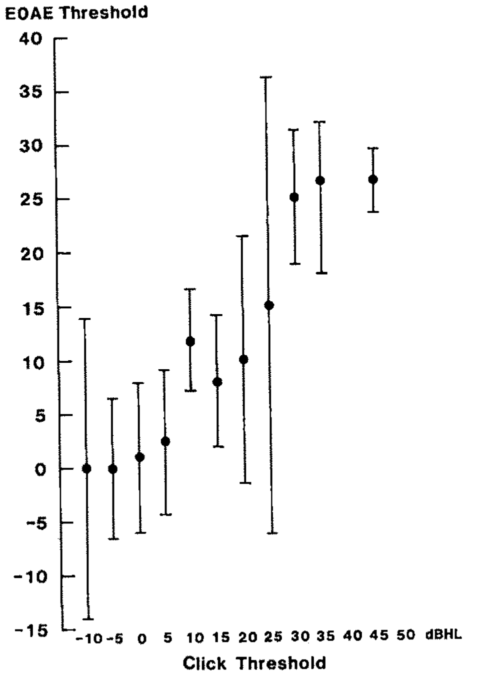

Fig 4. Evoked otoacoustic emission threshold according to click threshold.

(p<.0001). The difference between these thresholds increases with age (N = 138) (Fig 5): F (8,129) = 4.19 (p<.0001); r = −.37 (p<.0001).

Age Factor for Highest Frequency Peak in Spectral Analysis. Calculation concerned the frequency peak at 30 dB HL; this drops with age: F (8,146) = 3.76 (p<.0001) (Fig 6).

DISCUSSION

The present study confirms the results of Bonfils et al[24] demonstrating an age factor with respect to presence of EOAEs, their threshold, and the frequency of the highest frequency peak. This effect would seem to be related to an alteration in cochlear biomechanics and/or the reduction in number of hair cells with age — particularly noticeable in the OHCs.[23] That some elderly subjects do show EOAEs may be accounted for by the great variation in hair cell loss with age, as shown by cytocochleography.[23] It may be supposed that loss of hair cells leads to reduction in active contractional phenomena in the organ of Corti and hence to reduction in EOAEs. The results concerning the thresholds have to be discussed in terms of the validity of this parameter. From a technical point of view it seems to be only a question of measuring the phenomena down into the noise of the instrumentation. The effect of age on this parameter reflects in fact an effect of age on the amplitude of the EOAE. Rise in EOAE threshold was found to be more or less parallel to that of subjective perception. In itself, a rise in EOAE threshold would seem once again to correlate to hair cell loss. Indeed, Gleeson and Felix[27] have shown that hearing loss and age correlate closely with number of OHCs and inner hair cells.

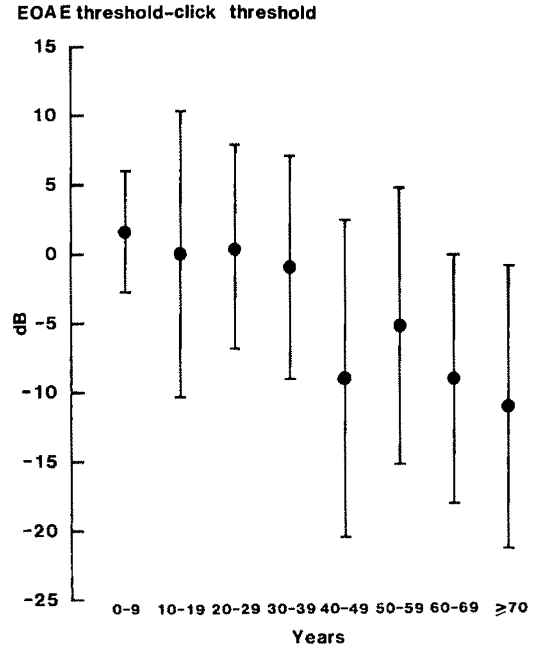

Fig 5. Difference between evoked otoacoustic emission threshold and click threshold according to age group.

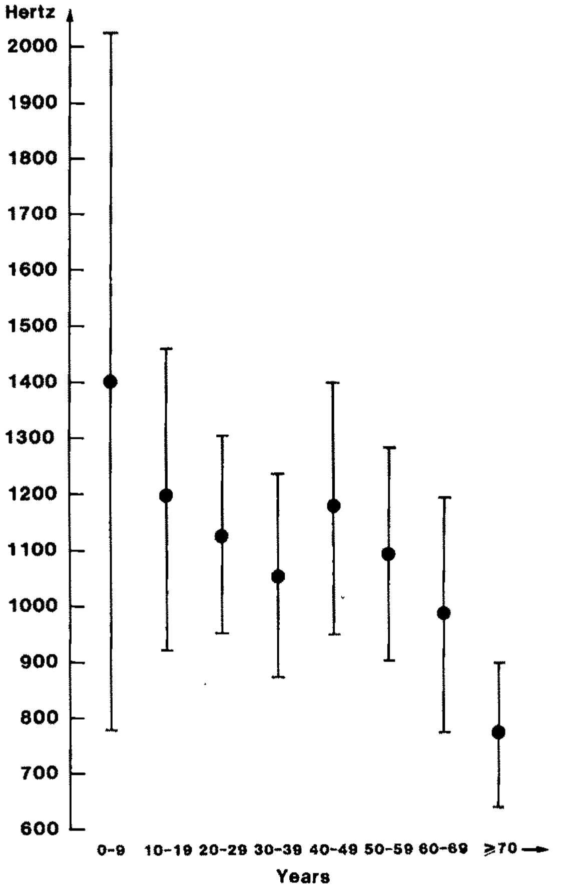

Fig 6. Peak frequency according to age group.

However, the difference found between the perceptual and EOAE thresholds corresponds to the fact that EOAEs are basically a function of OHC activity (more precisely of the active micromechanical properties of the cochlea), whereas the subjective perception threshold is a function of inner cell activity, synaptic efficiency, and neuronal conduction. There would thus seem to be distinct age effects upon neuronal and synaptic mechanisms on the one hand and upon cochlear mechanisms on the other. Finally, basal cell loss with age can account for the lower characteristic spectral analysis frequency peak in elderly subjects. Indeed, such basal cell loss may result in activation of more apical OHCs than in younger subjects. Norton and Neely[28] showed a close correspondence between stimulus and response spectrums, using tone-burst stimulation. It may thus be supposed that in older subjects, lower frequency components operate in EOAEs, which are thus of lower frequency. However, the discussion of hair cells and their relationship to hearing loss and emissions is open. Actually, the specific relationship between hair cell loss and otoacoustic emissions is not well known. Age and hearing loss probably interact to influence EOAE threshold and frequency characteristics. At the low end of the age spectrum the results may be discussed in terms of growth. The resonance characteristics of the external and middle ear apparatus change in 10 years, probably most notably in the first year or so. With such changes, the "click" is different on the way into the cochlea, and the echo should be different on the way out.

Our study has not shown any sex-linked factor in EOAEs (as in the work of Bonfils et al[24]). In auditory physiology there is controversy concerning a sex-linked factor in the various brain stem auditory evoked potential wave latencies. Several authors have pointed to shortenings of waves I and V and/or the I-III and I-V intervals.[28-31] Others consider sex-linked differences to be simply due to anatomic parameters — in particular to the smaller skull diameter of female compared to male subjects.[32]

In conclusion, age does have an effect upon EOAEs in humans that seems to be linked with an alteration of cochlear biomechanics and/or hair cell loss. For clinical applications,[2,33-35] such an effect has to be taken into consideration.

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IMMUNOHISTOCHEMICAL STUDY OF CYTOKERATIN EXPRESSION IN NORMAL AND PATHOLOGIC MIDDLE EAR MUCOSA OF THE RAT

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The expression of cytokeratins in the epithelium of the middle ear and external auditory meatus of the rat was studied on cryosections of ethylenediaminetetraacetic acid-decalcified specimens by use of a panel of monoclonal antibodies. The normal middle ear epithelium revealed a complex cytokeratin profile, including regional differences. The induction of sterile middle ear effusions resulted in increased cytokeratin expression. Infective effusions were accompanied by both quantitative and qualitative changes in the cytokeratin expression patterns. The difference observed between the cytokeratin profiles of external meatal skin and those of middle ear epithelium may form a useful tool for research into cholesteatoma development.

KEY WORDS — cytokeratins, middle ear effusions, middle ear epithelium.

INTRODUCTION

The epithelium of the middle ear cavity is composed of flat squamous epithelium and areas of ciliated epithelium. By far the largest part of the cavity is lined by flat epithelium, while the ciliated cells are arranged in tracts coursing from distinct areas in the middle ear toward the orifice of the eustachian tube.[1-3] From studies both on human biopsy samples and in animal models it has become clear that the middle ear epithelium can undergo considerable changes as a consequence of infection, inflammation, or eustachian tube obstruction.[1,4-6]

These changes, mainly consisting of increased secretory activity and occasionally squamous metaplasia,[1,5,7,8] are assumed to contribute to the development of chronic otitis media and its sequelae, but the pathogenesis of these processes is still poorly understood. Furthermore, although obstruction of the eustachian tube is generally considered an important etiologic factor in the pathogenesis of otitis media, its precise role in this process is still a matter of debate.[4,9]

A new approach in the study of cell differentiation that may help to further characterize the middle ear epithelium under normal and pathologic conditions is the study of intermediate filament proteins, which are important constituents of the intracellular cytoskeleton. In epithelial cells the intermediate filaments are composed of cytokeratins.[10]

Nineteen different types make up two major subgroups of basic and acidic cytokeratins that combine in pairs; 2 to 10 can be found in one individual cell. Their expression has been shown to depend on the type of epithelium, the stage of differentiation, and the functional state of a cell.[11] For example, cytokeratins 7, 8, 18, and 19 generally characterize simple epithelia. Cytokeratins 5 and 14 are commonly present in all stratified epithelia. In addition, in noncornifying epithelia cytokeratins 4 and 13, and in cornifying epithelia cytokeratins 1, 2, and 10 are found. They can be visualized by immunocytochemistry with use of specific antibodies.[12]

Until now, no precise data were available on the cytokeratin profile of the middle ear epithelium. The few available reports are limited to the study of biopsy samples obtained from cholesteatoma operations.[13-15] In this study a comprehensive analysis was made of the cytokeratin expression patterns in the epithelial lining of the middle ear of the rat. In addition, changes in this expression pattern caused by the induction of both sterile and infective middle ear effusions are described.

METHODS

The study was conducted on adult male Wistar rats (about 170 g body weight). For the induction of middle ear effusions, the models developed by Kuijpers et al[16] were used. In accordance with their method, eustachian tube obstruction was performed in the extratympanic course by electrocautery under Hypnorm anesthesia (intramuscular, 0.05 mL/100 g body weight) and diazepam (intraperitoneal, 0.05 mL/100 g body weight).

For obtaining sterile effusions, germ-free animals were operated upon. They were born and raised under sterile conditions, and for eustachian tube obstruction they were transferred from their sterile housing units to a laminar flow cabinet. Postoperatively, the animals were housed under specific pathogen-free conditions. Infective effusions were in-

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TABLE 1. CYTOKERATIN ANTIBODIES APPLIED

Antibody	*Specificity for Cytokeratin No.*	*Dilution*	*Reference*
RCK 102	5+8	Undiluted	18
RCK 103	5+?	1:2	18
RCK 105	7	Undiluted	18
RGE 53	18	Undiluted	12
CK 18-2	18	Undiluted	19
RKSE 60	10	1:2	18
LP 2K	19	Undiluted	20
1C7	13	Undiluted	21
6B10	4	Undiluted	21
pKer	Polyclonal	1:40	12

duced in animals carrying *Mycoplasma pneumoniae* in the upper respiratory tract.[16] A total of 10 animals were treated in each group, and five normal ears were used for control studies. After various periods of time ranging from 1 to 4 months, the animals were killed painlessly by an intracardiac injection of sodium pentobarbital (Nembutal) and subsequently decapitated.

For immunocytochemistry the region including the medial part of the external auditory meatus, the middle ear, and the inner ear was dissected and stored for 2 weeks at 4°C in 0.1 mol/L Tris hydrochloride buffer (pH 7.0) containing 10% ethylenediaminetetraacetic acid (EDTA) and 7.5% polyvinylpyrrolidone (PVP) for decalcification.[17] After rinsing for 2 hours in the same solution but without EDTA, the samples were frozen in liquid nitrogen and cryosectioned. In order to prevent rupturing of the mucosa in the air-filled control ears during sectioning, these ears were filled with a 15% gelatin solution in phosphate-buffered saline (PBS) before freezing. Sections were collected on poly-L-lysine–coated slides, quickly dried in a cold airstream, and stored at −80°C until required. For immunostaining the sections were fixed in acetone (10 minutes at 4°C), washed in PBS, and subsequently exposed to one polyclonal antibody and a panel of monoclonal antibodies, either as an undiluted culture supernatant or diluted in PBS (Table 1[12,18-21]) for 45 minutes in a moist chamber. All antibodies used in this study were raised against human proteins.

The sections were then washed in PBS and incubated for 30 minutes with horseradish peroxidase–conjugated rabbit anti mouse antibodies diluted 1:40 in PBS. After washing in PBS followed by sodium acetate buffer (0.05 mol/L, pH 4.9), the peroxidase activity was detected with use of 0.02% 3′amino-9′ethylcarbazole, 5% dimethylformamide, and 0.01% hydrogen peroxide in sodium acetate buffer. Control sections were incubated in the same buffer solution with omission of the primary antibody. The sections were counterstained with Harris' hematoxylin. Separate cryostat sections were fixed in formaldehyde and stained with hematoxylin and eosin for general histology. To study the effects on the immunodetection of cytokeratin after storage in the EDTA-PVP mixture necessary for decalcification, freshly dissected mucosa specimens were also included in the immunocytochemical procedures.

RESULTS

Normal Ear. The cytokeratin expression patterns of the normal middle ear epithelium are summarized in Table 2 and illustrated in Figs 1 through 4. For comparative purposes, the cytokeratin profile of the external meatal skin, including the epidermal lining of the tympanic membrane, is included in Table 2. The simple squamous epithelium revealed a homogeneous positive reaction to antibodies pKer, RCK 102, RCK 103, LP2K, and CK 18-2, although the staining with RCK 103 was rather weak at some sites (Figs 1 through 4). The antibodies RGE 53, 6B10 (Fig 2), and RCK 105 produced a heterogeneous staining pattern that was different for the various antibodies. At some sites only a few scattered cells were stained, especially on the promontory and on the tympanic membrane.

The ciliated secretory epithelium showed a strong positive reaction to antibodies LP2K, RCK 103 (Fig 3), RCK 102, RGE 53, and CK 18-2, although staining of the basal cells was found to occur only with RCK 103. A heterogeneous reaction was established with RCK 105, while antibody 6B10 failed to show any reaction in the tall ciliated cells (Fig 3). No reaction at all could be detected with antibodies RKSE 60 and 1C7.

The tympanic membrane and the epidermis of the external meatus, including the hair follicles and sebaceous glands, stained very positively with RCK 103 and pKer. With RKSE 60, only the suprabasal

TABLE 2. CYTOKERATIN EXPRESSION IN NORMAL MIDDLE EAR EPITHELIUM AND MEATAL SKIN OF RAT

	RCK 102	*RCK 103*	*RCK 105*	*RGE 53*	*CK 18-2*	*LP2K*	*1C7*	*6B10*	*RKSE 60*	*pKer*
Cytokeratin	5+8	5+?	7	18	18	19	13	4	10	
Meatal skin	−*	+ +	−	−	−	−	−	−	+ +†	+
Middle ear squamous epithelium	+	+	(+)	(+)	+ +	+ +	−	(+)	−	+ +
Mucociliary tract	+ +	+ §	(+)	+ +	+ +	+ +	−	−	−	+ +

− indicates negative, + indicates weakly positive, (+) indicates heterogeneous weak staining, + + indicates strongly positive.

*Positive cells were only in inner layer of root sheath of hair follicle.

†Only suprabasal layers were positive.

§Mainly basal cells were positive.

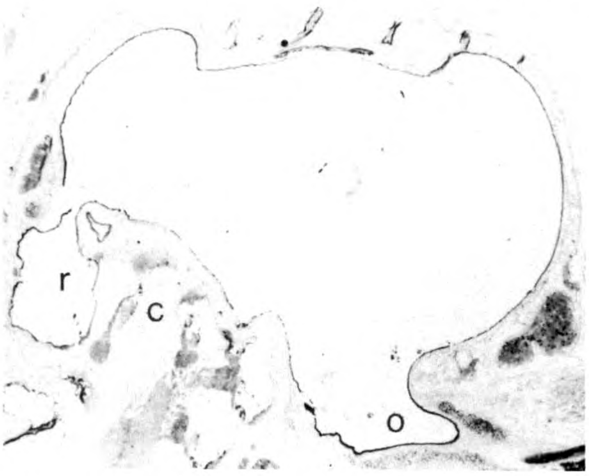

Fig 1. Cryosection of rat middle ear immunostained with monoclonal antibody RCK 102. o — orifice of eustachian tube, r — round window niche, c — cochlea.

layers stained, while with RCK 102, staining was limited to the inner layers of the root sheath of the hair follicles (Fig 4). All the other antibodies tested failed to show any positive reaction.

Comparison between specimens stored in EDTA and freshly dissected mucosae revealed no differences in the cytokeratin expression patterns. The staining intensity appeared to be even slightly stronger after EDTA treatment.

Serous Effusions. The course of events observed after eustachian tube obstruction in germ-free animals was identical to that described in earlier reports.[4] Within a few days after obstruction, the middle ear cavity became filled with a clear yellow fluid that persisted throughout the observation period of 4 months. The flat squamous epithelium showed increasing hypertrophy and hyperplasia as well as desquamation with the progression of time, whereas the ciliated epithelium remained virtually unaffected. The cytokeratin profile did not differ significantly from that in normal epithelium, but the staining intensity was much stronger. The basal cell layers of the hyperplastic epithelium showed a positive reaction only with RCK 103; with 6B10 it was limited to a few scattered cells (Fig 2).

Two germ-free animals in this group developed a short transient middle ear infection during the first week after occlusion, as was diagnosed by otoscopy. This occasionally occurs and is likely to be explained by invasion of bacteria through the cauterized area when the animals are kept under specific pathogen–free conditions.[22] This short-term infection could be confirmed by the histologic sections

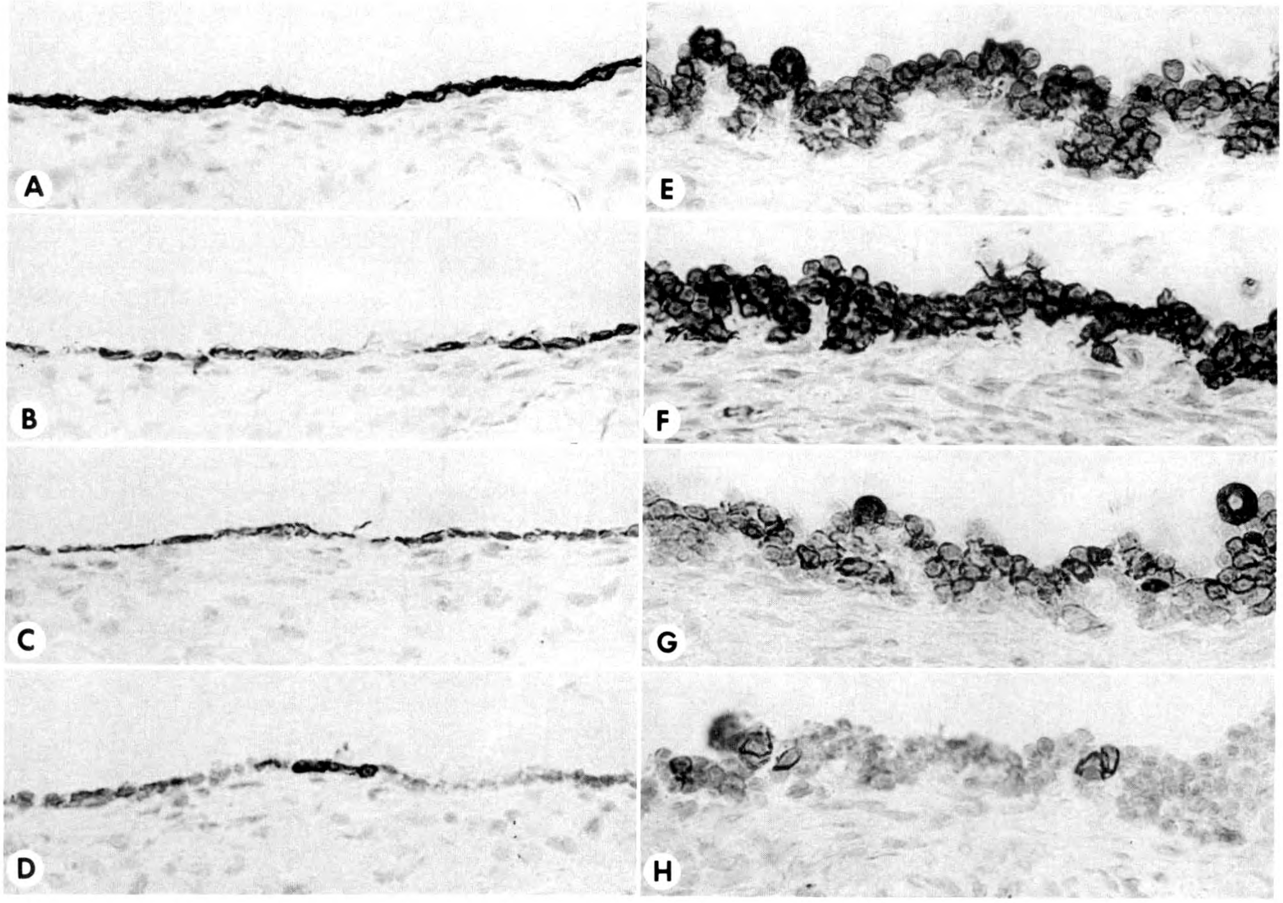

Fig 2. Immunohistochemical staining profiles of flat squamous epithelium, obtained with different monoclonal antibodies A-D) in control ear and E-H) 4 months after induction of sterile serous effusion. A,E) RCK 102. B,F) RCK 103. C,G) RGE 53. D,H) 6B10.

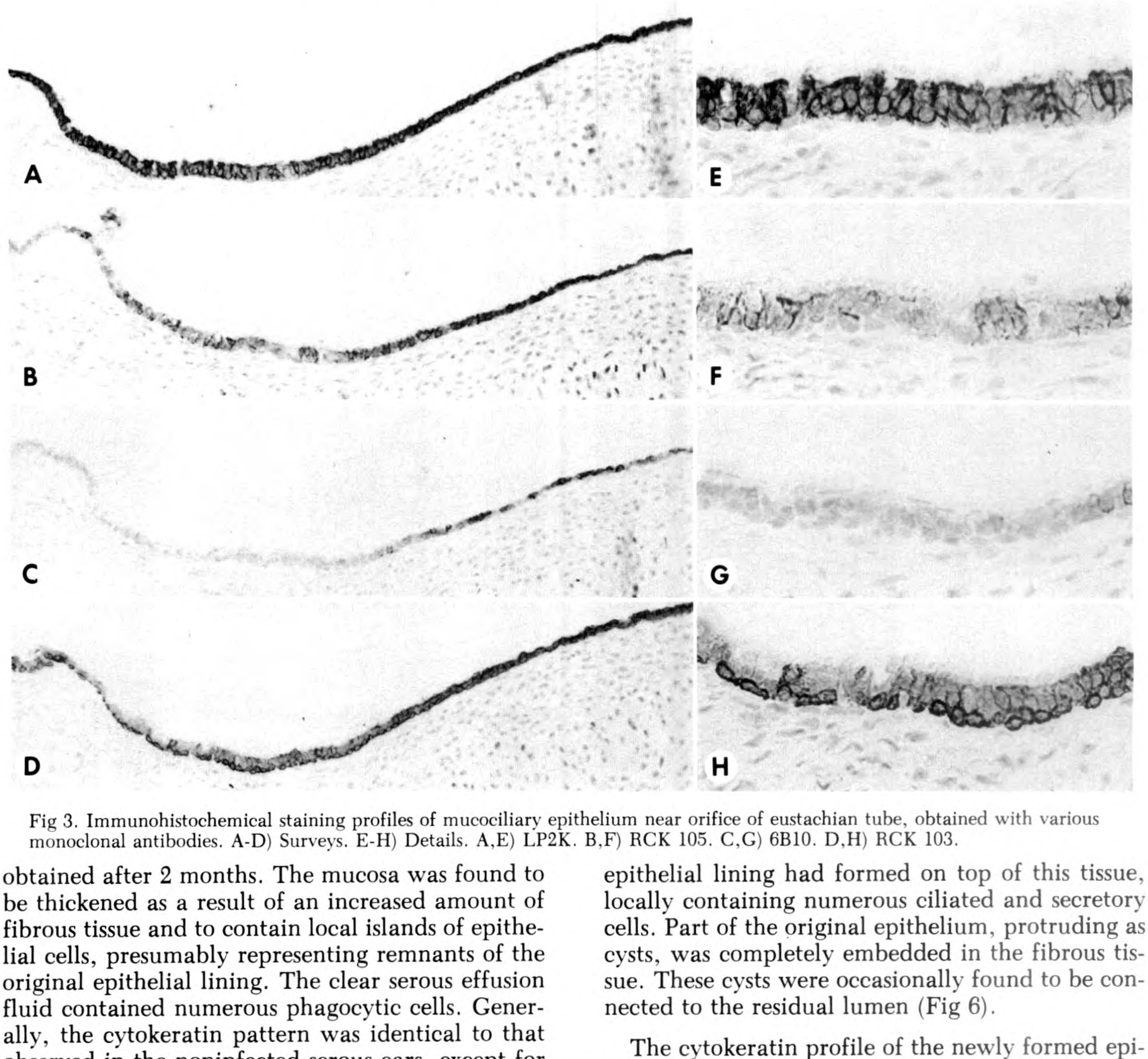

Fig 3. Immunohistochemical staining profiles of mucociliary epithelium near orifice of eustachian tube, obtained with various monoclonal antibodies. A-D) Surveys. E-H) Details. A,E) LP2K. B,F) RCK 105. C,G) 6B10. D,H) RCK 103.

obtained after 2 months. The mucosa was found to be thickened as a result of an increased amount of fibrous tissue and to contain local islands of epithelial cells, presumably representing remnants of the original epithelial lining. The clear serous effusion fluid contained numerous phagocytic cells. Generally, the cytokeratin pattern was identical to that observed in the noninfected serous ears, except for the remnants of the original epithelium embedded in the mucosa. In these areas often no reaction was found to antibodies RCK 105 and 6B10, whereas staining with RGE 53 differed from site to site. Only the staining patterns with RCK 102 and RCK 103 were similar to those in the epithelial lining (Fig 5).

Infected Effusions. All animals carrying *M pneumoniae* in the upper respiratory tract developed infective middle ear disease within a few days after obstruction, and it persisted throughout the observation period. Routine histology generally revealed that the changes induced by the infection varied among different animals, but no clear relationship could be established between the condition of the middle ear and the duration of the infection.

Some ears showed a middle ear cavity filled with purulent debris and extensive destruction of the mucosa, while in other specimens the cavity was obliterated to various degrees with fibrous tissue. A new epithelial lining had formed on top of this tissue, locally containing numerous ciliated and secretory cells. Part of the original epithelium, protruding as cysts, was completely embedded in the fibrous tissue. These cysts were occasionally found to be connected to the residual lumen (Fig 6).

The cytokeratin profile of the newly formed epithelium of both the simple squamous and the ciliated secretory cells was qualitatively similar to that in the normal ears, but staining was more intense. However, the cytokeratin profile of the original epithelium, embedded in the fibrous tissue, demonstrated some remarkable changes. Normal staining was observed with antibodies RCK 102, RCK 103, and CK 18-2, but staining with RCK 105 and 6B10 was often absent in these areas, and staining with RGE 53 or LP2K generally differed from site to site (Fig 6). These observations were made in all specimens studied, although individual differences were seen.

DISCUSSION

This immunocytochemical study demonstrates that the epithelium of the normal middle ear shows complex cytokeratin distribution patterns that are completely different from those of the cornifying epithelium of the external meatus. All antibodies to

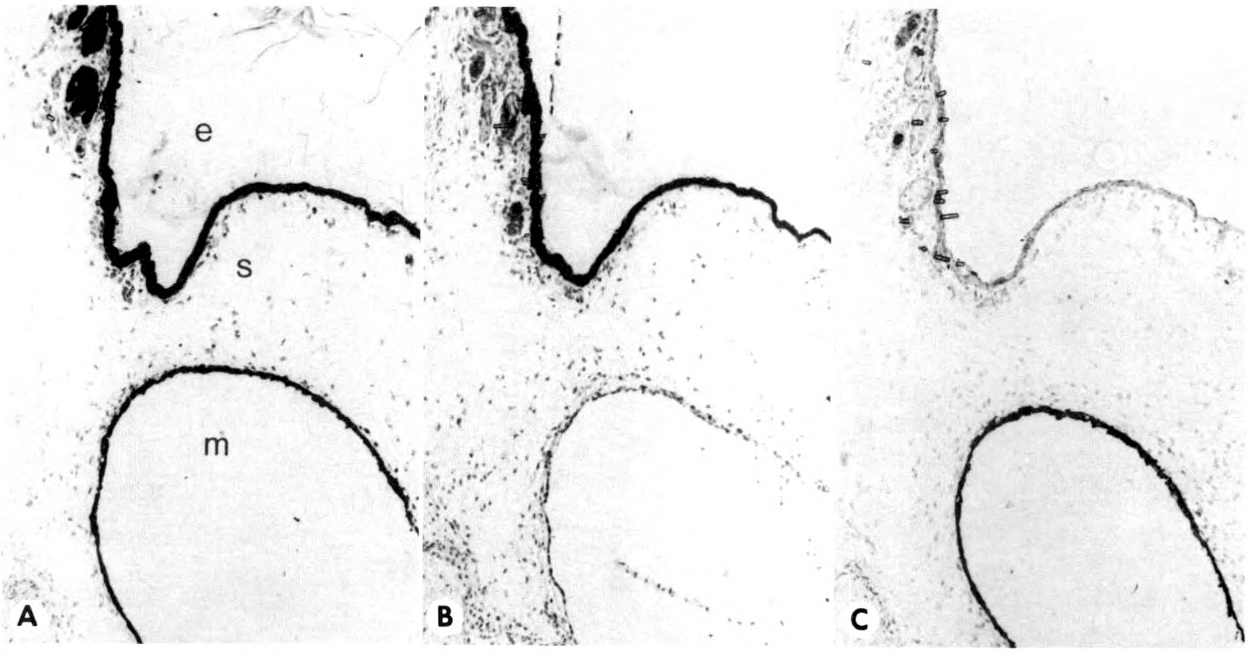

Fig 4. Expression of cytokeratins in epithelium of external meatus (e) and middle ear (m), obtained with monoclonal antibodies A) RCK 103, B) RKSE 60, and C) RCK 102. s — pars flaccida.

human cytokeratins that were applied in this study exhibited the tissue specificity that has been previously found in human and rat tissues.[23,24]

The expression of cytokeratins 7, 8, 18, and 19 is in line with the reports on comparable epithelia in other parts of the respiratory tract, such as the pseudostratified epithelium of the bronchi and the simple alveolar epithelium,[25] as well as with the general rules formulated for simple epithelia.[11,26] The same holds for the expression of cytokeratin 10 (RKSE 60), which is a specific marker for cornifying epithelia.[18] In contrast to the ciliated epithelium in the bronchi,[25] cytokeratin 4, which could be demonstrated with antibody 6B10, is virtually absent in the ciliated epithelium of the middle ear.

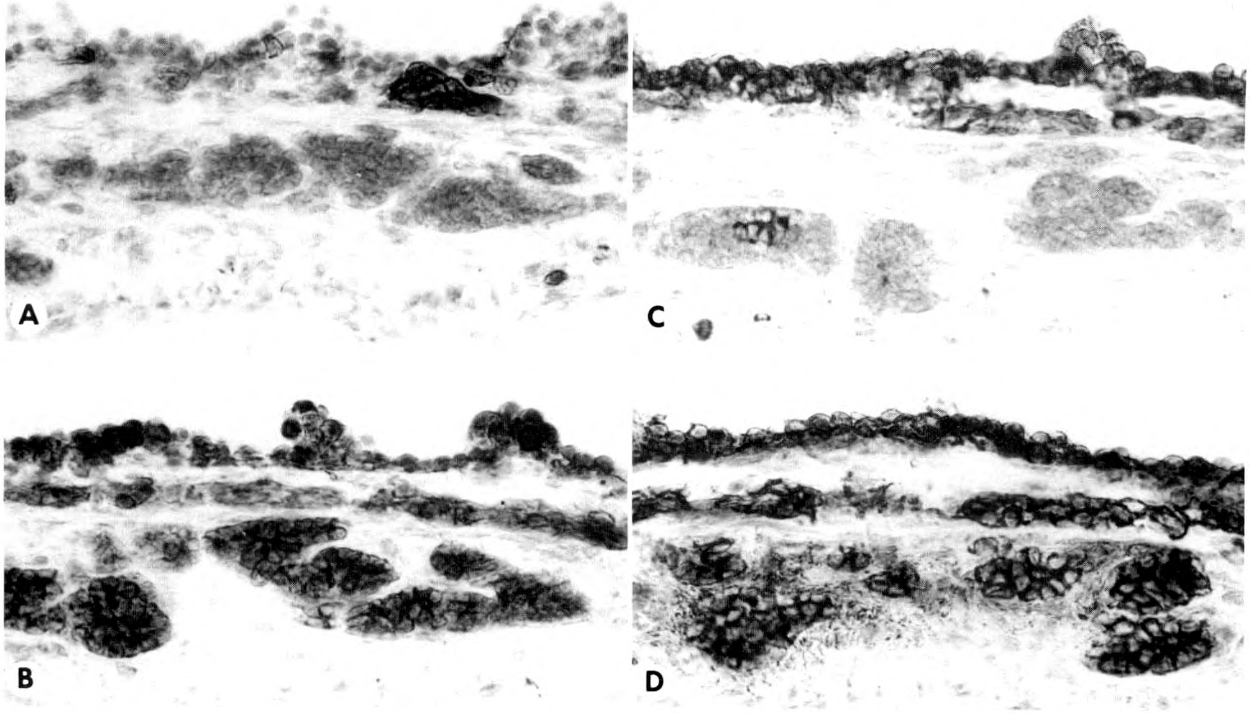

Fig 5. Expression of cyokeratins in squamous epithelium 4 months after induction of serous effusion. This ear had short transient infection during first week after obstruction. Note difference in expression between epithelial lining and subepithelial cystlike structures. A) 6B10. B) RGE 53. C) RCK 105. D) RCK 102.

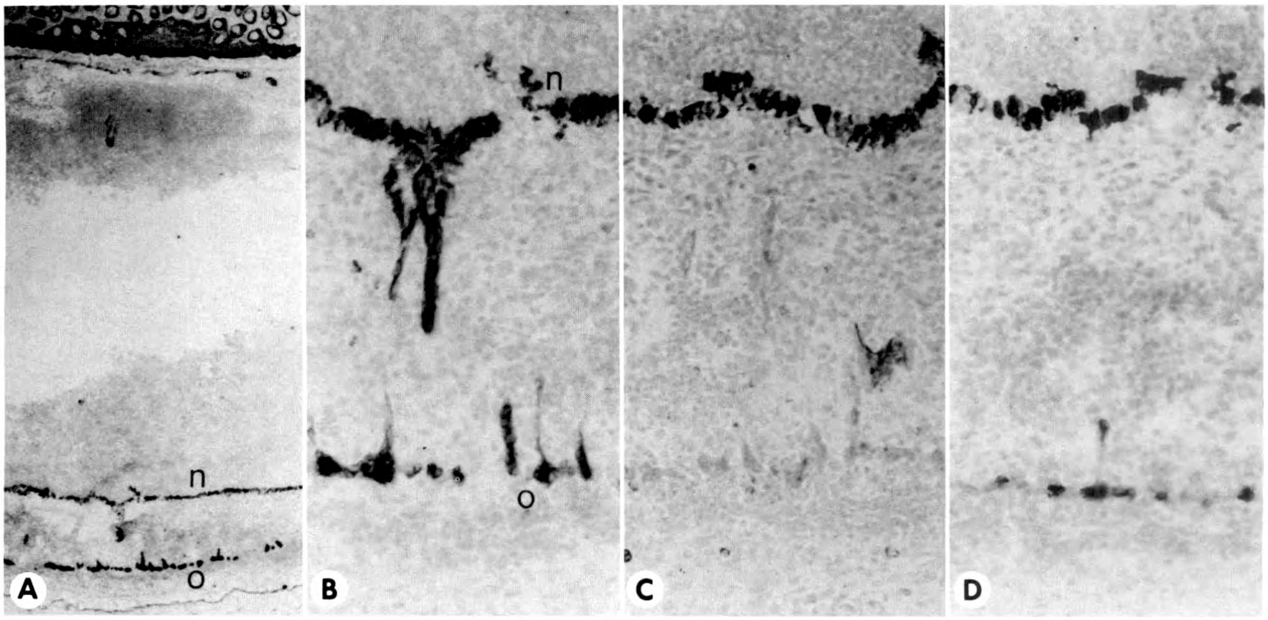

Fig 6. Immunohistochemical staining profiles of middle ear epithelium obtained with various antibodies 4 months after induction of infective middle ear effusion. Note difference in expression between original (o) and newly formed (n) epithelium. A) Survey. RCK 103. B-D) Higher magnification. B) RCK 102. C) RCK 105. D) RGE 53.

Remarkably, antibodies RCK 105 (cytokeratin 7) and 6B10 (cytokeratin 4) showed regional differences in the cytoskeleton of flat epithelium. These data demonstrate a more heterogeneous composition of the middle ear epithelium than is known from electron microscopic data.

The epitopes of RCK 103 have not yet been fully elucidated, but the staining patterns obtained in the squamous epithelium and basal cells were in agreement with the observations made by Feitz et al[23] and Verhage et al.[24]

Although RGE 53 and CK 18-2 are both specific for cytokeratin 18, fewer cells were stained by RGE 53. This difference might be ascribed to the configuration of the epitope. Epitope masking has been convincingly described by Franke et al.[27]

The induction of sterile middle ear effusions by eustachian tube obstruction does not result in qualitative changes in the cytokeratin profile, but the expression of most of the cytokeratins tested was strongly increased. This coincides with the development of cell hypertrophy and an increase in the number of tonofilaments, which is in agreement with previous findings.[22] Staining of the basal cell layers of the hyperplastic epithelium with RCK 103 was in accordance with established findings of basal cell hyperplasia.[22]

Conspicuous changes in the expression of cytokeratin were observed after the induction of infective middle ear effusions. Although the newly formed epithelial lining displayed the same basic pattern of cytokeratin expression as the normal epithelium, the expression of the preexistent epithelium showed conspicuous changes. This is a remarkable observation, because changes in the expression of cytokeratin in simple epithelia have only been observed under in vitro conditions.[11]

In summary, our findings demonstrate that the composition of the middle ear epithelium may be more complex than has been established so far on the basis of morphologic studies. In addition, the induction of middle ear effusions can result in both qualitative and quantitative changes in the cytokeratin profile, the significance of which is unknown. Finally, the difference in cytokeratin expression observed between the epidermis of the meatal skin and the middle ear epithelium might prove helpful for research into cholesteatoma development.

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SIXTH WORLD CONGRESS IN ULTRASOUND

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Ann Otol Rhinol Laryngol 99:1990

IMAGING CASE STUDY OF THE MONTH

SPONTANEOUS PNEUMOPERICARDIUM AND PNEUMOMEDIASTINUM

NODAR BARTAL, MD

SULEIMAN ZAARURA, MD HAROLD MARVAN, MD

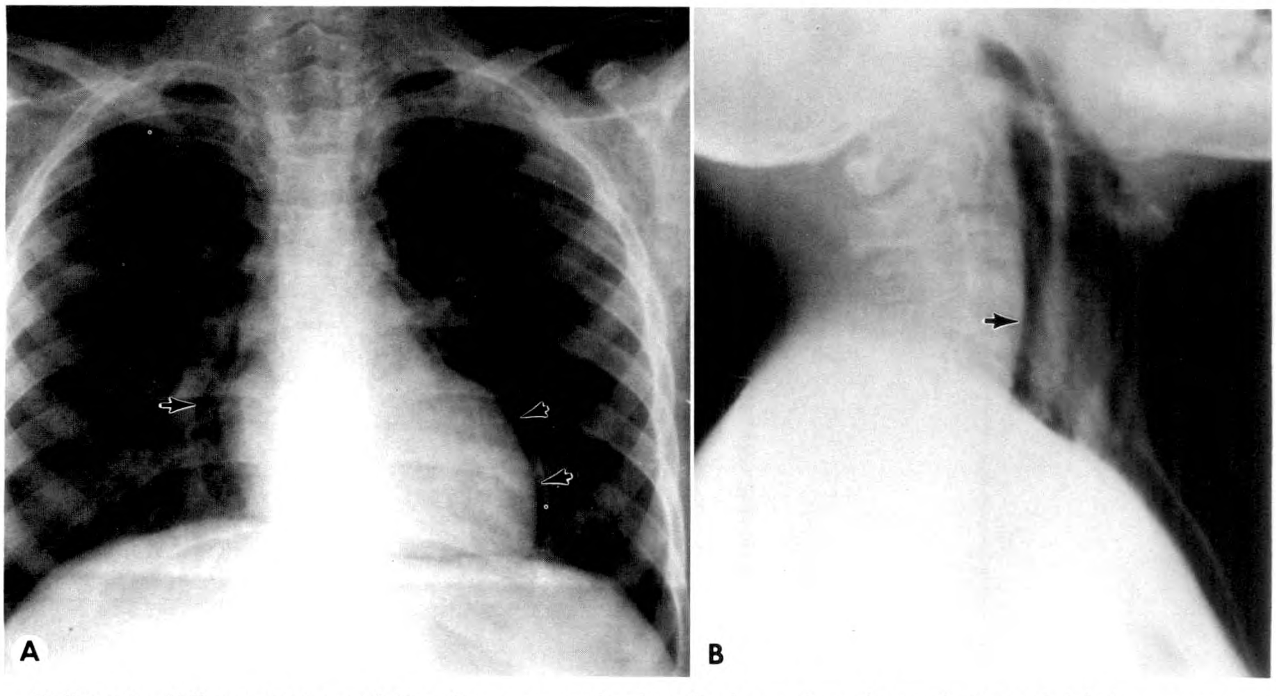
TIBERIAS, ISRAEL

A 10-year-old boy was brought to the emergency room in respiratory distress. He was in good health until he awoke in the night because of severe cough. He suddenly felt a pain in the chest and experienced difficulty in breathing. On examination the patient was slightly cyanotic and dyspneic, with "ballooning" of the soft tissue of the neck. Palpation revealed subcutaneous emphysema of the neck and upper chest. Additionally there was severe bulging of the posterior pharyngeal wall and bilateral pulmonary wheezing. The radiographic findings are shown in the Figure.

After the diagnosis of spontaneous pericardial and mediastinal emphysema the boy was prescribed bed rest in a semisitting position. Intravenous cefazolin sodium 3.0 g per day was started. A 100-mg daily dose of intramuscular hydrocortisone sodium succinate was given for 2 days. The hospitalization period was uneventful. The boy was discharged in good health 12 days following hospitalization. Control radiographs were within normal limits.

DISCUSSION

Spontaneous pneumopericardium and pneumomediastinum, sometimes called pericardial or mediastinal emphysema, is a very rare condition with a multitude of possible causes: athletics, parturition, pulmonary barotrauma, severe cough, asthma, cocaine inhalation, chlorine gas exposure, and emesis.[1-3] Alveolar rupture as a result of a sudden increase of intrapulmonary pressure is the port of entry of the air into the mediastinum. The exact mechanism by which the air reaches the mediastinal and pericardial spaces was an enigma for a long time. Today it is commonly accepted that the air dissects along the perivascular spaces to enter the



Radiographs. A) Demonstrating gentle line of air, corresponding heart borders, and vascular vessels. Pericardial thickening is seen in right lower border of heart (arrowheads). B) Demonstrating presternal subcutaneous emphysema and free air in fascial spaces of neck (arrowhead).

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REPRINTS — Nodar Bartal, MD, ENT Unit, Poriya Government Hospital, Tiberias, 15208, Israel.

mediastinum. From here it can decompress into the subcutaneous tissues, the deep cervical spaces, and eventually the pericardial space.[1] Other causes of the disease are direct trauma of the upper digestive tract, neoplasm disrupting the mucosal integrity of the esophagus, gas-producing infection, and even achalasia.[4]

The acute onset of retrosternal pain radiating to the back, neck, or shoulders is a usual clinical manifestation of the mediastinal phase of the disease. Mediastinal crepitation (Hamman's sign) is the classic physical finding at this stage. It may be accompanied by cardiac dullness on auscultation.[4] When the air reaches the deep cervical spaces, pressure on the upper airway can create respiratory distress, as was the case with our patient.

If the process continues and dissecting air enters the pericardial space, cardiovascular dynamics may be compromised. Fatal tension pneumopericardium with air cardiac tamponade has been reported.[5]

The symptoms of mediastinal emphysema alone may mimic those of pericardial emphysema. Therefore, radiographic evidence of air in the pericardial space is the pathognomonic sign that must be present to establish conclusively the diagnosis of pneumopericardium.[6]

There are no pathognomonic electrocardiographic findings for pericardial emphysema, and the appearance of the echocardiogram can mimic that of pericardial effusion.[6]

Spontaneous mediastinal and pericardial emphysema is almost always a self-limited condition. Treatment, which accompanies a diligent search for possible etiologic factors, consists of supportive measures: oxygen, analgesics, sedation, and careful monitoring. Most patients will recover within 1 to 2 weeks, as ours did.

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Ann Otol Rhinol Laryngol 99:1990

PATHOLOGY CONSULTATION

HISTOPATHOLOGIC GRADING OF SALIVARY GLAND NEOPLASMS: III. ADENOID CYSTIC CARCINOMAS

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Histopathologic grading of adenoid cystic carcinomas can provide valuable prognostic information, particularly when the presence or absence of a solid growth architecture is noted. Other growth patterns, exemplified by a tubuloductal or cribriform-cylindromatous differentiation, are associated with a more protracted biologic course and less rapid mortality. A three-tiered grading system based on the three growth patterns of the carcinoma is presented.

If histopathologic grading of adenoid cystic carcinoma is less controversial than the grading of other salivary carcinomas, it may be that certain cytomorphologic features of the carcinoma are not completely aleatory to size, site, clinical stage, and completeness of resection of the neoplasm.

That a solid growth architecture in an adenoid cystic carcinoma imparts a more serious prognosis than any other architecture was first suggested a half century ago.[1] The validity of the observation has been underscored in subsequent studies and in the event has placed the solid adenoid cystic carcinoma (see Figure, A) at the histologically defined high-grade end of the neoplasm's light microscopic spectrum.[2-9] At the opposite or low-grade end of the spectrum is the tubular or tubuloductal adenoid cystic carcinoma (see Figure; B,C). The "classic" or cribriform-cylindromatous pattern lies between. These three cytoarchitectures form the basis of nearly every grading scheme for adenoid cystic carcinoma. Mode of invasion (broad front or pushing versus diffuse or tentacular), perineurial invasion, mitotic activity, necrosis, and cellular and nuclear pleomorphism are additional findings often incorporated in the grading of the carcinoma.[10]

Eneroth et al,[2,3] in dealing with adenoid cystic carcinoma at two different sites, the palate and submandibular gland, demonstrated that the solid form of the carcinoma was associated with a high mortality and, especially, a considerably shorter survival time than cribriform carcinomas. Using determinate survival statistics, Eneroth et al[2] found a 17% survival at 5 years and no survivors at 10 years for patients with solid adenoid cystic carcinomas of the palate. Cribriform carcinomas manifested 100% and 62% survival at 5 and 10 years, respectively. A fulminating course with early recurrence, metastasis, and a fatal outcome within 3 years of therapy also characterized the behavior of solid adenoid cystic carcinomas reported by Eby et al.[4] Patients without solid-type carcinomas had a prolonged course with survival for many years in spite of recurrences and metastases. Morinaga et al[5] have also shown that the prognosis of adenoid cystic carcinoma with a solid pattern is worse than that without in respect to 5- and 10-year survival rates. At 15 years, however, there was no difference between the two groups. The effect of a solid pattern on cumulative survival rates is also seen in data presented by Szanto et al.[6] Dividing their adenoid cystic carcinomas into three grades based on the presence and preponderance of a solid component, these authors found cumulative survival rates at 15 years of 39% (no solid), 26% (less than 30% solid), and 5% (preponderantly solid). The carcinomas with a preponderantly solid architecture were larger, recurred frequently, and killed their hosts within 4 years. A solid cellular pattern negatively affected the survival period of adenoid cystic carcinomas of the maxillary sinus in the analysis reported by Buffoli et al.[11] The preponderantly solid carcinomas were also associated with a higher T stage than nonsolid carcinomas.

The incidence of lymphatic (noncontiguous involvement) metastases to regional lymph nodes from adenoid cystic carcinomas is known to be low. When present, the metastases have a dramatically adverse effect on survival. Stell et al[12] have indicated that such metastases occur more often in poorly differentiated (solid) adenoid cystic carcinomas. They also state that site and stage are not significant predictors of the probability of the metastases.

In 1978, Perzin et al[7] described and introduced to surgical pathologists what they believed to be the most differentiated form of adenoid cystic carcinoma — the tubular pattern. Classifying 62 carcinomas according to their predominant histologic pat-

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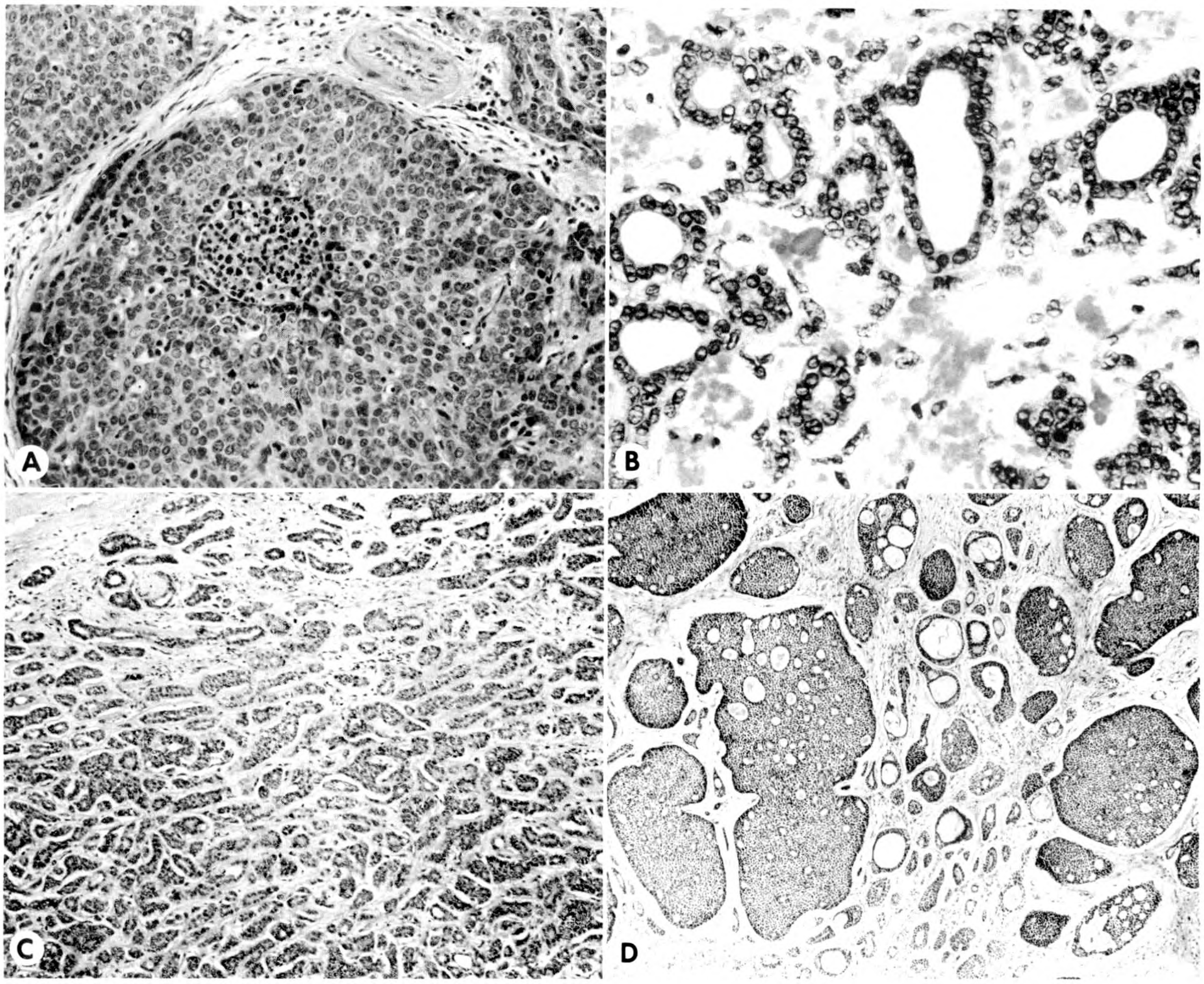

Adenoid cystic carcinomas. A) Solid form, manifesting no differentiation, central necrosis, mitoses, and cellular or nuclear pleomorphism (H & E, original x200). B) Tubular form, manifesting small ductal lumens and rather banal cytomorphology (H & E, original x200). C) Tubuloductal form, with tentacular invasion and invasion of small nerve (upper left) (H & E, original x60). D) Manifesting preponderantly solid growth pattern but with areas of cribriform differentiation (H & E, original x60). This coexistence of patterns is common, with assigned grade based on dominant pattern in carcinoma.

tern (tubular, cribriform, or solid), these investigators found a recurrence rate of 59% with carcinomas demonstrating a preponderantly tubular pattern, as compared to 89% for the cribriform lesions and 100% for solid carcinomas. Of patients who died of their malignancy, those with tubular carcinomas had the longest course (average 9 years before death, in contrast to 8 years for cribriform and 5 years for solid carcinomas). Chilla et al[8,9] have subsequently confirmed the distinctly favorable course exhibited by tubular adenoid cystic carcinomas.

The foregoing suggests that histopathologic grading of adenoid cystic carcinoma has prognostic implications, especially as it relates to the carcinoma's two extremes of differentiation — tubular and solid. However, the greater importance of the clinical stage and its often linear relationship with the grade have prompted Spiro et al[13-15] to reserve judgment of the impact of histologic appearance on prognosis.

The three grades of adenoid cystic carcinoma proposed in the Table represent a composite of criteria used by several other proponents of grading. Data reported by Caselitz et al[16] give an immunohistologic profile of the three basic cytoarchitectural patterns of the grades that, in turn, supports the reserve cell hypothesis of the histogenesis of the carcinomas.[17]

Histologic grading should ideally be prospective, be applied to carcinomas presenting in a single anatomic region or salivary gland that are similarly staged, and be reproducible. Since the three basic growth patterns of adenoid cystic carcinoma are uncommon in a pure form, the assigned numeric grade has reflected the dominant pattern (see Figure, D). This subjective evaluation may suffice for carcinomas with tubular and cribriform-cylindromatous architectures, but the repeated demonstrations of poor patient outcome associated with a solid pattern require a more objective assessment. Szanto

THREE GRADES OF ADENOID CYSTIC CARCINOMA AND THEIR HISTOCYTOLOGIC CHARACTERISTICS

Grade 1	*Grade 2*	*Grade 3*
Often circumscribed and usually smaller than other grades; may manifest capsule	May be deceptively circumscribed and, on rare occasions, encapsulated, particularly in major salivary glands	Never circumscribed or encapsulated
Pushing, blunt, or diffuse infiltrative growth; perineurial invasion of small nerves can be present	Infiltrative growth is usual; more perineurial invasion than grade 1	Infiltrative growth, nearly always diffuse; perineurial invasion readily identified
Definite tubular or ductal architecture; can simulate ductal monomorphic adenoma or terminal duct adenocarcinoma; cytologically banal; no or very rare mitoses	Cribriform and cylindromatous architecture; few to rare mitoses; cytologically less banal than grade 1; polymorphism and pleomorphism of cells mild to moderate	Solid sheets and nests of atypical basaloid cells; "undifferentiated" appearance; mitoses easily found
Stromal changes usually not conspicuous; hyalinization not common; no necrosis	Stromal changes usually prominent and may be striking; excessive hyalinization may obscure carcinoma; focal necrosis may be present	Variable stromal induction; necrosis easily found and may be comedo type
Rarely present in pure form; usually coexists with cribriform-cylindromatous pattern	Can present in pure form; if coexisting with tubular form, tubules exhibit more atypia than seen in usual grade 1	Rarely present in pure form, and if so, may not be recognizable as adenoid cystic carcinoma; most often coexists with grade 2 phenotype

et al[6] and Greiner et al[18] have elected a 30% solid component to signify a high-grade adenoid cystic carcinoma in their grading proposals. It is possible, however, that any measurable solid component in an otherwise cribriform or tubular adenoid cystic carcinoma portends a worse prognosis and shorter survival periods.

While the impact of a solid architecture on patient outcome is strong, there is considerably less certainty of the significance of ***histologic*** evidence of perineurial invasion as it relates to survival. An absence of correlation has been reported by most investigators of the problem.[4-6,18-20] In none of the studies, however, has the size of the invaded nerve been given. It may be that small nerve invasion, found in any of the three grades, does not carry the stigma of probable therapeutic failure seen in patients with preoperative facial nerve dysfunction.

In view of the data derived from other grading systems for adenoid cystic carcinoma, it may be that the most important derivative of grading will be to identify those carcinomas with a rapidly progressive and lethal course. Other patients will manifest the traditionally accepted high morbidity and delayed mortality regardless of the level of differentiation or clinical stage.

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BOOK REVIEWS

Neurophysiology of the Vestibular System

E. Pirodda, O. Pompeiano, editors. Volume 41 in *Advances in Oto-Rhino-Laryngology*. C. R. Pfaltz, editor-in-chief. Hard cover, illustrated, indexed, 243 pages, 1988. S. Karger, Basel, Switzerland.

This volume of *Advances in Oto-Rhino-Laryngology* contains 44 selected papers from the Barany Society Meeting in Bologna, Italy, July 1-4, 1987. A subsequent volume of 61 clinical papers on the vestibular system will be forthcoming, but its table of contents is included in this volume. The scope of these papers ranges from aspects of basic science of the vestibular system to clinical investigational studies of vestibular tests. Obviously, the value of this volume varies with its multiple topics, authors, and the reader's background information. This collection of papers presumes preexisting knowledge of the vestibular system and clinical vestibular testing modalities, eg, rotary chair testing of vestibulo-ocular reflex (VOR).

The first four papers present results of cellular neurophysiologic and morphologic studies of the vestibular system, which this clinician found enlightening, with the caveat that the clinical application is pending. I found ingenious Mamoru Suzuki's work utilizing the semicircular canal cupula to stimulate the macular sensory epithelia for confirmation of physiologic polarity.

Several subsequent papers report investigations of whole-body rotation testing of VOR. Other papers in this subgroup include studies of velocity storage mechanisms, VOR adaptive changes, and saccadic eye movements. Material by Laurence R. Harris on horizontal velocity storage and Hideharu Aoki on VOR gain changes with magnification affecting optokinetic reflex gain control elicited reader interest because of their lucid, informative introductions. Included is the work of Alain Berthoz et al reporting that otolith-derived information concerning head linear displacement can be stored for retrieval of the brain. Also available is R. Schmid's clear discussion of vestibulo-saccadic pathways, suggesting that the fast phase of nystagmus represents the active part of quickly resetting the object of interest, in contrast to an emphasis on reestablishing a "central" position.

Activity of the vestibular neurons, the relation of vestibular mechanisms and impaired vestibular function on postural control, and righting reflexes are explored in subsequent papers. I. Pyykko's investigation on geriatric posture control and K. Kaga's study on infants with labyrinthine hypoactivity provide clinical counterpoint to preceding basic science papers. Vestibulo-ocular analysis with the vestibular autorotation high-frequency test as a variant of VOR rotational chair testing (Dennis P. O'Leary) and test-retest rotating test reliability (Herman A. Jenkins) are among the last group of topics that deal with enhancing accuracy of VOR testing.

The section on magnetic resonance imaging of the posterior fossa with emphasis on the vestibular system reviews material familiar to those clinicians with experience with this imaging modality. In contrast, papers concerned with vascular disease and the vestibular system integrate several evaluation methods in an intriguing manner for this reader. C. Sabban's paper notes the effect of vascular artery compression in electroencephalographic cartography, and saccadic eye movements in patients with hemodynamic vertebrobasilar insufficiency. This noninvasive technique demonstrates hypermetria, thought to be associated with cerebellar disease, and hypometria, best appreciated with brain stem, cerebellar, and basal ganglion ischemia. The degree of EEG changes was related to the duration and severity of vertebrobasilar insufficiency. Correlation of these objective findings with subjective symptoms is not available.

The majority of the papers in this volume are well illustrated, and their tables are clear. A satisfactory index is available, but an author index is absent (the table of contents lists the authors). Overall, the articles are lucid and concise. Some papers are more notable for their enlightening introductions, which engage more interest and participation by the reader. This is especially helpful, since there are no editorial comments or recapitulations of the discussions following the initial presentation of these papers at the Barany Society Meeting. Such comments can assist the less-informed resident or clinician in placing these isolated papers into a more meaningful perspective.

In summary, this collection of papers is a series of extended abstracts best directed to the basic science or clinical researcher involved with the vestibular system. Editorial comments would have expanded the readership appeal. This edition will be most appreciated in departmental libraries and personal libraries of those pursuing this type of research. It is anticipated that the companion volume of clinical papers will be of greater interest to the clinician or resident.

PAUL E. HAMMERSCHLAG, MD
New York, New York

Granulomas and Neoplasms of the Larynx

Imrich Friedmann and Alfio Ferlito. Hard cover, illustrated, indexed, 357 pages, 1988. Churchill Livingstone, Edinburgh, Scotland.

This is a pathology text written by pathologists who are well known worldwide for their specialization, dedication, and expertise in the field of otolaryngology and head and neck pathology. Dr Ferlito has particularly specialized in the pathology of the larynx. Their experience has led to a compact, easily read, particularly complete and current publication on the pathology of tumors of the larynx.

The text consists of 30 chapters with appropriate dedication to the anatomy and histology of the larynx. Techniques of biopsy and congenital pathology of the larynx are covered. Nine chapters are dedicated to inflammatory, granulomatous, and nonneoplastic tumefactions involving the larynx. The remaining chapters discuss all the neoplastic entities that one would ever expect to encounter in the larynx. The individual neoplastic entities are presented in a uniform format with paragraphs dealing generally with definition, historical aspect, incidence, clinical aspects, histogenesis, gross and histologic features, and current conceptions of treatment and prognosis. The most recent information on diagnostic immunohistology is particularly appreciated. Probably one of the more helpful aspects of this text are the bibliographies that accompany each chapter. They are sufficient and certainly current. The only deficiency that is rather glaring is the poor reproduction of many of the photographs, particularly the histologic ones.

I would definitely recommend this text to otolaryngologists, from residents to experienced practitioners. I would also think that pathologists, whether general or specializing in the head and neck area, would find this volume most helpful.

VINCENT J. HYAMS, MD
Washington, DC

Boies Fundamentals of Otolaryngology

George L. Adams, Lawrence R. Boies, Jr, and Peter A. Hilger. Hard cover, illustrated, indexed, 539 pages, 1989. WB Saunders, Philadelphia, Pa, $65.

Boies Fundamentals of Otolaryngology is the sixth edition of this basic textbook. Much of the text has been rewritten and new illustrations, charts, and photographs have been added. The book covers the major areas in otolaryngology and includes a thorough, clearly written chapter on the head and neck examination. The authors have designed this latest edition to comply with medical school curricula, and it provides the medical student with a solid foundation in the diagnosis and management of the more common problems in otolaryngology.

STEPHEN G. ROTHSTEIN, MD
New York, New York

ANNALS OF OTOLOGY, RHINOLOGY & LARYNGOLOGY

ANNALS OF HEAD & NECK MEDICINE & SURGERY®

— *Founded in 1892* —

Volume 99
January-December 1990
Issues 1-12, Supplements 144-151

Published by
ANNALS PUBLISHING COMPANY
4507 LACLEDE AVENUE
ST LOUIS, MISSOURI 63108

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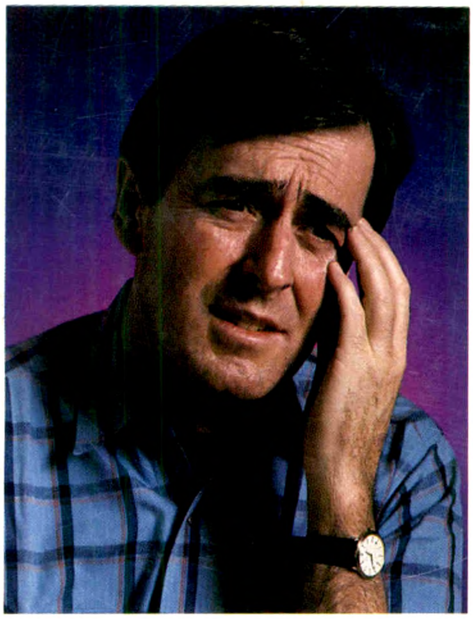

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